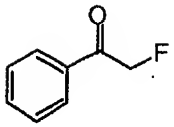
4-piperidylpyrrolo[3,2-*d*]pyrimidine as a yellow colored solid.

Example 150: 1-[4-(2-Methyl-4-piperidylpyrrolo [4,5-*d*]pyrimidin-6-yl)phenyl]ethan-1-one (188 mg, 0.60 mmol) was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.60 mL, 0.60 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 104 mg (4%) of Example 150 as a yellow colored solid. Mp: 173.5-175 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.65 (br s, 6), 2.51 (s, 3), 2.57 (s, 3), 4.01 (br s, 4), 6.98 (s, 1), 8.05 (q, 4, *J* = 4.5), 12.02 (s, 1), 14.31 (s, 1). MS *m/z*: 335 (M+1 for free base). Anal. Calcd for $C_{20}H_{22}N_4O \cdot HCl \cdot 1.75H_2O$: C, 56.69; H, 6.64; N, 13.93; Cl, 8.81. Found: C, 59.78; H, 6.53; N, 14.00; Cl, 8.91.

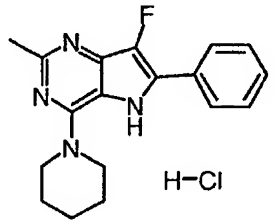
Example 151: 2-Methyl-6-[4-(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenyl]-4-piperidylpyrrolo[3,2-*d*]pyrimidine (76 mg, 0.20 mmol) was dissolved in 5:2 EtOAc/MeOH (15 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.40 mL, 0.40 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum at 60 °C to give 30 mg (1%) of Example 151 as a yellow colored powder. Mp: >280 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.66 (br s, 12), 2.52 (s, 6), 4.02 (br s, 8), 6.96 (s, 2), 8.05 (s, 4), 12.01 (s, 2), 14.21 (s, 2). MS *m/z*: 507 (M+1 for free base). Anal. Calcd for $C_{30}H_{34}N_8 \cdot 2HCl \cdot 4H_2O$: C, 55.29; H, 6.81; N, 17.20; Cl, 10.88. Found: C, 54.96; H, 6.62; N, 16.74; Cl, 11.00.



Example 152

(a) 2-Fluoro-1-phenylethan-1-one.

A mixture of 2-bromoacetophenone (Aldrich Chemical Company) (5.42 g, 27.3 mmol), KF (6.32 g, 0.11 mol) and 18-crown-6 (3.61 g, 13.7 mmol) in CH_3CN (150 mL) was heated at 90 °C for 16 h under a N_2 atmosphere. Heating was discontinued and the mixture was allowed to cool to room temperature. The mixture was diluted with H_2O (300 mL) and EtOAc (400 mL) and transferred to a separatory funnel. The organic solution was separated, washed with H_2O (2 x 300 mL), saturated NaCl (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude ketone (3.02 g) was used without further purification (see Gregory et al. *J. Med. Chem.* 1990, *33*(9), 2569).



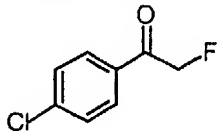
(b) 7-Fluoro-2-methyl-6-piperidylpyrrolo[3,2-*d*] pyrimidine Hydrochloride.

To a room temperature solution of [2-fluoro-1-phenylvinyl]pyrrolidine (freshly prepared before use from 2-fluoro-1-phenyl ethan-1-one (Example 152(a)), pyrrolidine and $TiCl_4$ (see Example 30) (2.44 g, 12.7 mmol) in anhydrous toluene (15 mL) was added *N,N*-diisopropylethylamine (Aldrich Chemical Company) (2.0 mL, 12.7 mmol) followed by 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.61 g, 12.7 mmol). After stirring at room temperature for 2.5 h the reaction mixture was filtered through a fritted funnel.

The residue was washed with hot toluene (2 x 30 mL) and the filtrate was concentrated under reduced pressure. The residue was dissolved with dioxane/toluene (20 mL:10 mL) and NEt_3 (Aldrich Chemical Company) (2.1 mL) and piperidine (Aldrich Chemical Company) (2.0 mL, 20.3 mmol) were added. The mixture was stirred at 80 °C for 2 h under a N_2 atmosphere. The $SnCl_2$ solution was added to the reaction mixture at 80 °C. The mixture was stirred at 80 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The reaction mixture was poured onto a mixture of NaOH (5g) and crushed ice (150 mL) and stirred for 1 h. The resulting slurry was filtered through a Celite® pad, the pad was rinsed with 10:1 EtOAc/MeOH (4 x 60 mL). The filtrate was transferred to a seperatory funnel. The organic solution was separated, washed with H_2O (3 x 350 mL), saturated NaCl (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 0.51 g (13%) of 7-fluoro-2-methyl-6-piperidylpyrrolo[3,2-*d*]pyrimidine as a brown colored foam. This compound (0.51 g, 1.60 mmol) was dissolved in 10:1 EtOAc/MeOH (35 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.60 mL, 1.60 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 270 mg (6%) of the title compound as pale green colored needles. Mp: >280 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.72 (br s, 6), 2.59 (s, 3), 4.07 (br s, 4), 7.53-7.57 (m, 1), 7.61 (t, 2, J = 7.7), 7.87 (d, 2, J = 7.5), 12.07 (s, 1), 14.56 (s, 1). MS *m/z*: 311 (M+1 for free base). Anal. Calcd for

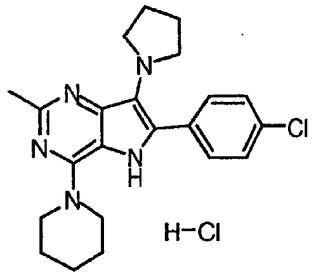
$C_{18}H_{19}FN_4 \bullet HCl$: C, 62.33; H, 5.81; N, 16.15; Cl, 10.22. Found: C, 62.04; H, 5.95; N, 16.08; Cl, 10.02.

Example 153



(a) 1-(4-Chlorophenyl)-2-fluoroethan-1-one.

Using the method described in Example 152(a) by employing 2-bromo-4'-chloroacetophenone (Aldrich Chemical Company) (4.06 g, 17.5 mmol), KF (4.1 g, 0.11 mol) and 18-crown-6 (3.61 g, 13.7 mmol). The resulting crude ketone was used without further purification.

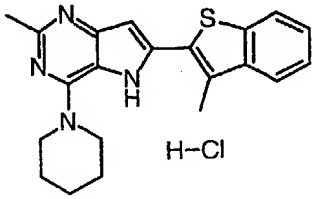


(b) 2-Methyl-6-phenyl-4-piperidyl-7-pyrrolidinyl pyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing [1-(4-chlorophenyl)-2-fluorovinyl]pyrrolidine (freshly prepared before use from 1-(4-chlorophenyl)-2-fluoroethan-1-one (Example 153(a)), pyrrolidine and $TiCl_4$ (see Example 30) (3.00 g, 13.3 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.80 g, 13.3 mmol), *N,N*-diisopropylethylamine (2.3 mL, 13.3 mmol), piperidine (2.1 mL, 21.3 mmol), NEt_3 (2.2 mL) and $SnCl_2$ (40 mL of a 2 M soln in DMF). In this example, the $SnCl_2$ solution was added to the reaction mixture at 140 °C. (Note: When both the piperidine displacement and the $SnCl_2$ reduction sequences are performed at 140 °C the pyrrolidine moiety is incorporated). The mixture was stirred at 140 °C for

an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 0.38 g (8%) of 2-methyl-6-phenyl-4-piperidyl-7-pyrrolidinylpyrrolo[3,2-*d*]pyrimidine as a brown colored solid. This compound (0.38 g, 1.00 mmol) was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.00 mL, 1.00 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum at 60 °C to give 162 mg (2%) of the title compound as a beige colored powder. Mp: >280 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.49 (br s, 2), 1.54 (br s, 4), 1.88 (br s, 2), 2.01 (br s, 2), 2.59 (s, 3), 2.92 (br s, 4), 3.72 (br s, 2), 4.04 (br s, 2), 7.57 (d, 2, J = 8.5), 7.76 (d, 2, J = 8.4), 11.44 (s, 1), 13.13 (s, 1). MS *m/z*: 396 (M+1 for free base). Anal. Calcd for $C_{22}H_{26}ClN_4 \cdot HCl \cdot 0.5H_2O$: C, 59.86; H, 6.39; N, 15.87; Cl, 16.06. Found: C, 59.56; H, 6.36; N, 15.70; Cl, 15.95.

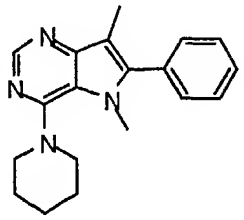
Example 154



3-Methyl-2-[2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl]benzo[*b*]thiophene Hydrochloride Hydrate.

Using the method described in Example 30 by employing 3-methyl-2-(1-pyrrolidinylvinyl)benzo[*b*] thiophene (freshly prepared before use from 2-acetyl-3-methylthianaphthene (Avocado Chemical Company),

pyrrolidine and $TiCl_4$ (1.67 g, 6.88 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.43 g, 6.88 mmol), *N,N*-diisopropylethylamine (1.2 mL, 6.88 mmol), piperidine (1.1 mL, 11.0 mmol), NEt_3 (1.5 mL) and $SnCl_2$ (21 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3$/MeOH as eluant to give 0.60 g (24%) of 3-methyl-2-[2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]benzo[*b*]thiophene as a beige colored solid. This compound (596 mg, 1.64 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.70 mL, 1.70 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 421 mg (16%) of the title compound as a pale yellow colored powder. Mp: >280 °C. ^1H NMR (DMSO-d_6; 400 MHz): δ 1.65 (br s, 6), 2.46 (s, 3), 2.51 (s, 3), 3.98 (br s, 4), 6.67 (s, 1), 7.41-7.47 (m, 2), 7.87 (dd, 1, *J* = 1.7, 6.2), 7.99 (dd, 1, *J* = 1.7, 6.4), 12.43 (s, 1), 14.38 (s, 1). MS *m/z*: 363 (M+1 for free base). Anal. Calcd for $C_{21}H_{22}N_4S \cdot HCl \cdot 0.4H_2O$: C, 62.10; H, 5.91; N, 13.80; Cl, 8.73. Found: C, 62.04; H, 5.92; N, 13.80; Cl, 8.83.

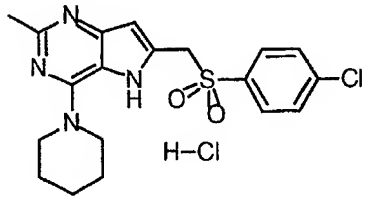


Example 155

5,7-Dimethyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*] pyrimidine.

To a 0 °C solution of 7-methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (Example 89) (177.3 mg, 0.61 mmol) in THF (10 mL) under a nitrogen atmosphere was added LiHMDS (1.0 M soln from Aldrich Chemical Company) (1.3 mL, 1.27 mmol). This mixture was stirred at 0 °C for 0.5 h then CH_3I (Aldrich Chemical Comapny) (41 mL, 0.67 mmol) was added. The 0 °C bath was removed and the solution stirred at room temperature for 2.5 h. The reaction mixture was poured into a separatory funnel containing EtOAc (35 mL) and H_2O (50 mL). The organic solution was collected washed with H_2O (3 x 40 mL), saturated NaCl (70 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified via flash chromatography on silica gel 95:5 $CHCl_3$/MeOH as eluant to give 164 mg (86%) of the title compound as a beige colored solid. Mp: 123.0-125.0 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.68 (m, 2), 1.78 (m, 4), 2.30 (s, 3), 3.42 (br s, 4), 3.66 (s, 3), 7.44-7.54 (m, 5), 8.61 (s, 1). MS *m/z*: 307 (M+1).

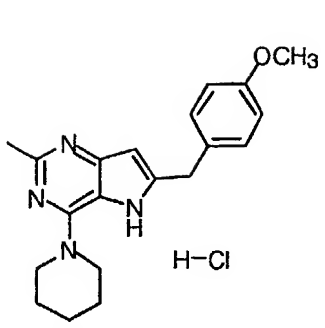
Example 156



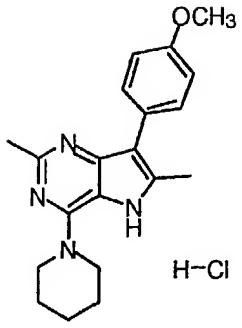
4-Chloro-1-[((2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl)methyl)sulfonyl]benzene Hydrochloride Hydrate.

Using the method described in Example 30 by employing 1-[(2-pyrrolidinylprop-1-enyl)sulfonyl]-4-

chlorobenzene (freshly prepared before use from 4-chlorophenylsulfonylacetone (Lancaster Chemical Company), pyrrolidine and $TiCl_4$ (2.03 g, 7.10 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.47 g, 7.10 mmol), *N,N*-diisopropylethylamine (1.3 mL, 7.10 mmol), piperidine (1.1 mL, 11.4 mmol), NEt_3 (1.6 mL) and $SnCl_2$ (21 mL of a 2 M soln in DMF). In this example the mixture of enamine, 2-methyl-4,6-dichloro-5-nitropyrimidine and *N,N*-diisopropylethylamine was stirred at 100 °C for 20 h prior to piperidine addition. The $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 100% EtOAc as eluant to give 441 g (15%) of 4-chloro-1-[((2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)methyl)sulfonyl] benzene as a brown colored solid. This compound (0.44 g, 1.08 mmol) was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.10 mL, 1.10 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 296 mg (9%) of the title compound as a white colored solid. Mp: 199-201 °C. ^1H NMR (DMSO-d_6; 400 MHz): δ 1.57 (m, 4), 1.65 (m, 2), 2.47 (s, 3), 3.85 (br s, 4), 5.02 (s, 2), 6.23 (s, 1), 7.65 (AB q, 4, *J* = 6.2, 6.2), 12.20 (s, 1), 14.18 (s, 1). MS *m/z*: 405 (M+1 for free base). Anal. Calcd for $C_{19}H_{21}ClN_4O_2S \cdot HCl \cdot 0.9H_2O$: C, 49.87; H, 5.24; N, 12.25; Cl, 15.49. Found: C, 49.85; H, 5.17; N, 12.15; Cl, 15.61.



Example 157



Example 158

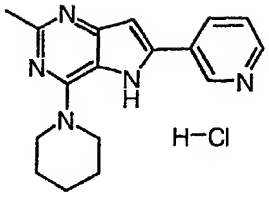
Example 157 and Example 158

4-Methoxy-1-[(2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl)methyl]benzene Hydrochloride and 1-[2,6-Dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-7-yl]-4-methoxybenzene Hydrochloride Hydrate.

Using the method described in Example 30 by employing 1-[2-pyrrolidinylprop-1-enyl]-4-methoxy benzene (freshly prepared before use from 4-methoxy phenylacetone (Aldrich Chemical Company), pyrrolidine and $TiCl_4$ (3.06 g, 14.10 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.92 g, 14.10 mmol), *N,N*-diisopropylethylamine (2.5 mL, 14.10 mmol), piperidine (2.2 mL, 22.6 mmol), NEt_3 (3.1 mL) and $SnCl_2$ (42 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 578 g (12%) of 4-methoxy-1-[(2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl)methyl]benzene as a brown colored solid and 466 mg (10%) of 1-[2,6-dimethyl-4-piperidylpyrrolo [3,2-*d*]pyrimidin-7-yl]-4-methoxybenzene as a beige colored solid.

Example 157: 4-Methoxy-1-[(2-methyl-4-piperidyl pyrrolo[4,5-*d*]pyrimidin-6-yl)methyl]benzene (574 mg, 1.71 mmol) was dissolved in 5:1 EtOAc/MeOH (40 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.70 mL, 1.70 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 488 mg (9%) of Example 157 as tan colored crystals. Mp: 263-267 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.73 (br s, 6), 3.75 (s, 3), 4.01 (br s, 4), 4.15 (s, 2), 6.19 (s, 1), 6.94 (d, 2, J = 8.7), 7.27 (d, 2, J = 8.6), 12.02 (s, 1), 13.93 (s, 1). MS *m/z*: 337 (M+1 for free base). Anal. Calcd for $C_{20}H_{24}N_4O$•HCl: C, 64.42; H, 6.76; N, 15.03; Cl, 9.51. Found: C, 64.41; H, 6.66; N, 15.00; Cl, 9.63.

Example 158: 1-[2,6-Dimethyl-4-piperidylpyrrolo [3,2-*d*]pyrimidin-7-yl]-4-methoxybenzene (466 mg, 1.39 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.40 mL, 1.40 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 375 mg (7%) of Example 158 as a beige colored powder. Mp: 170 °C (dec). ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.62 (br s, 6), 2.36 (s, 3), 2.46 (s, 3), 3.76 (s, 3), 3.95 (br s, 4), 7.03 (d, 2, J = 8.7), 7.28 (d, 2, J = 8.6), 12.11 (s, 1), 13.27 (s, 1). MS *m/z*: 337 (M+1 for free base). Anal. Calcd for $C_{20}H_{24}N_4O$•1.2HCl•0.9H_2O: C, 60.60; H, 6.87; N, 14.14; Cl, 10.73. Found: C, 60.74; H, 6.62; N, 14.01; Cl, 10.62.



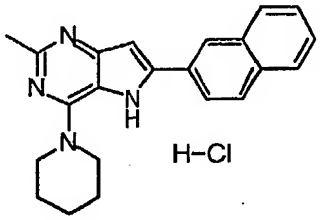
Example 159

2-Methyl-4-piperidyl-6-(3-pyridyl)pyrrolo[3,2-*d*] pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing 3-(1-pyrrolidinylvinyl)pyridine (freshly prepared before use from 3-acetylpyridine (Aldrich Chemical Company), pyrrolidine and $TiCl_4$ (1.95 g, 11.2 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.32 g, 11.2 mmol), *N,N*-diisopropylethylamine (2.0 mL, 11.2 mmol), piperidine (1.8 mL, 17.9 mmol), NEt_3 (2.5 mL) and $SnCl_2$ (34 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 0.5 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The mixture was stirred at room temperature an additional 4 d. The residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3$/MeOH as eluant to give 0.90 mg (3%) of 2-methyl-4-piperidyl-6-(3-pyridyl)pyrrolo[3,2-*d*] pyrimidine as a beige colored solid. This compound (89 mg, 0.30 mmol) was dissolved in 10:1 EtOAc/MeOH (10 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.30 mL, 0.30 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum at 60 °C to give 54 mg (2%) of the title compound as a brown colored solid. Mp: >280 °C. ^1H NMR (DMSO-d_6; 500 MHz): δ 1.65 (br s, 6), 2.51 (s, 3),

4.02 (t, 4, J = 5.4), 6.96 (s, 1), 7.52 (dd, 1, J = 7.9, 7.9), 8.32 (d, 1, J = 8.0), 8.61 (d, 1, J = 4.8), 9.11 (d, 1, J = 2.1), 12.08 (s, 1), 14.29 (s, 1). MS m/z: 294 (M+1 for free base). Anal. Calcd for $C_{17}H_{19}N_5 \bullet 1.05HCl \bullet 1.5H_2O$: C, 56.90; H, 6.48; N, 19.52; Cl, 10.37. Found: C, 57.20; H, 6.23; N, 19.50; Cl, 10.39.

Example 160

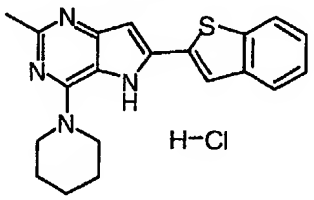


2-Methyl-6-(2-naphthyl)-4-piperidylpyrrolo[3,2-*d*] pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing [1-(2-naphthyl)vinyl]pyrrolidine (freshly prepared before use from 2'-acetylnaphthone (Aldrich Chemical Company), pyrrolidine and $TiCl_4$ (1.91 g, 8.60 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.78 g, 8.60 mmol), *N,N*-diisopropylethylamine (1.5 mL, 8.6 mmol), piperidine (1.4 mL, 13.8 mmol), NEt_3 (1.9 mL) and $SnCl_2$ (23 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 2.5 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The mixture was stirred at room temperature an additional 36 h. The residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3$/MeOH as eluant to give 1.25 g (55%) of 2-methyl-6-(2-naphthyl)-4-piperidylpyrrolo[3,2-*d*] pyrimidine as a beige colored solid. This compound (1.25 g, 3.64 mmol) was dissolved in 5:1 EtOAc/MeOH (60 mL) and heated to boiling. To the hot solution was

added 1 M ethereal HCl (3.60 mL, 3.60 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 1.02 g (40%) of the title compound as a yellow colored powder. Mp: >280 °C. ^1H NMR (DMSO-d_6; 400 MHz): δ 1.67 (br s, 6), 2.52 (s, 3), 4.04 (t, 4, J = 4.9), 6.98 (s, 1), 7.55 (m, 2), 7.94 (t, 1, J = 4.0), 8.00 (d, 1, J = 5.4), 8.02 (br s, 2), 8.50 (s, 1), 12.09 (s, 1), 14.27 (s, 1). MS m/z: 343 (M+1 for free base). Anal. Calcd for $C_{22}H_{22}N_4 \cdot HCl \cdot 1.5H_2O$: C, 65.09; H, 6.46; N, 13.81; Cl, 8.73. Found: C, 65.00; H, 66.45; N, 13.80; Cl, 8.76.

Example 161

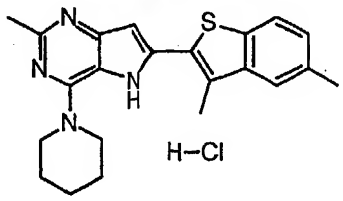


2-[2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl] benzo[*b*]thiophene Hydrochloride Hydrate.

Using the method described in Example 30 by employing 2-(1-pyrrolidinylvinyl)benzo[*b*]thiophene (freshly prepared before use from 2-acetylbenzo[*b*] thiophene (Avocado Chemical Company), pyrrolidine and $TiCl_4$ (1.71 g, 7.45 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.54 g, 7.45 mmol), *N*,*N*-diisopropylethylamine (1.3 mL, 7.45 mmol), piperidine (1.2 mL, 11.9 mmol), NEt_3 (1.7 mL) and $SnCl_2$ (22 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue

was purified by flash chromatography on silica gel with 95:5 $CHCl_3$/MeOH as eluant to give 1.04 g (40%) of 2-[2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]benzo[*b*]thiophene as a yellow colored powder. This compound (1.04 g, 2.98 mmol) was dissolved in 5:1 EtOAc/MeOH (50 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (3.00 mL, 3.00 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 0.88 g (31%) of the title compound as a yellow colored powder. Mp: >280 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.66 (br s, 6), 2.51 (s, 3), 4.00 (br s, 4), 6.74 (s, 1), 7.39 (m, 2), 7.91 (t, 1, *J* = 6.9), 8.00 (t, 1, *J* = 4.0), 8.16 (s, 1), 12.22 (s, 1), 14.21 (s, 1). MS *m/z*: 349 (M+1 for free base). Anal. Calcd for $C_{20}H_{20}N_4S \cdot HCl \cdot 0.70H_2O$: C, 60.42; H, 5.68;. N, 14.10; Cl, 8.92. Found: C, 60.38; H, 5.56; N, 13.93; Cl, 9.03.

Example 162

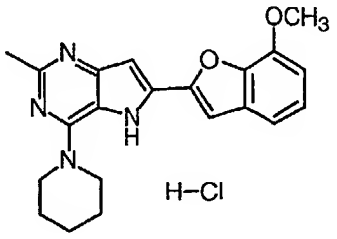


3,5-Dimethyl-2-[2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]benzo[*b*]thiophene Hydrochloride Monohydrate.

Using the method described in Example 30 by employing 3,5-dimethyl-2-(1-pyrrolidinylvinyl)benzo[*b*]thiophene (freshly prepared before use from 2-acetyl-3,5-dimethyl[*b*]thiophene (Avocado Chemical Company), pyrrolidine and $TiCl_4$ (1.81 g, 7.04 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.46 g,

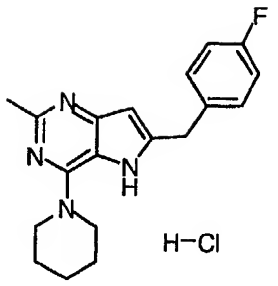
7.04 mmol), *N,N*-diisopropylethylamine (1.2 mL, 7.04 mmol), piperidine (1.1 mL, 11.3 mmol), NEt_3 (1.5 mL) and $SnCl_2$ (21 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3$/MeOH as eluant to give 0.53 g (20%) of 3,5-dimethyl-2-[2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]benzo[*b*]thiophene as a cream colored solid. This compound (530 mg, 1.41 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.50 mL, 1.50 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 493 mg (17%) of the title compound as a yellow colored solid. Mp: >280 °C. ^1H NMR (DMSO-d_6; 400 MHz): δ 1.64 (br s, 6), 2.43 (s, 3), 2.44 (s, 3), 2.51 (s, 3), 3.98 (br s, 4), 6.65 (s, 1), 7.27 (d, 1, *J* = 8.2), 7.66 (s, 1), 7.87 (d, 1, *J* = 8.3), 12.31 (s, 1), 14.13 (s, 1). MS *m/z*: 377 (M+1 for free base). Anal. Calcd for $C_{22}H_{24}N_4S \cdot HCl \cdot H_2O$: C, 61.31; H, 6.31; N, 13.00; Cl, 8.23. Found: C, 61.26; H, 5.92; N, 12.91; Cl, 8.32.

Example 163

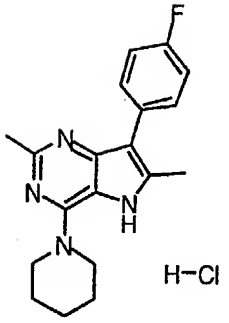


7-Methoxy-2-[2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl]benzo[*b*]furan Hydrochloride Hydrate.

Using the method described in Example 30 by employing 7-methoxy-2-(1-pyrrolidinylvinyl)benzo[*b*] furan (freshly prepared before use from 2-acetyl-7-methoxybenzo[*b*]furan (Avocado Chemical Company), pyrrolidine and $TiCl_4$ (1.89 g, 7.77 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.61 g, 7.77 mmol), *N,N*-diisopropylethylamine (1.4 mL, 7.77 mmol), piperidine (1.2 mL, 12.4 mmol), NEt_3 (1.7 mL) and $SnCl_2$ (23 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3$/MeOH as eluant to give 0.27 g (10%) of 7-methoxy-2-[2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]benzo[*b*]furan as a brown colored powder. This compound (0.26 g, 0.72 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.80 mL, 0.80 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 195 mg (7%) of the title compound as a yellow colored powder. Mp: >280 °C. ^1H NMR (DMSO-d_6; 400 MHz): δ 1.66 (br s, 6), 2.51 (s, 3), 3.92 (s, 3), 4.01 (br s, 4), 6.88 (s, 1), 6.98 (d, 1, *J* = 9.6), 7.20 (t, 1, *J* = 7.8), 7.28 (d, 1, *J* = 7.7), 7.72 (s, 1), 12.31 (s, 1), 14.09 (s, 1). MS *m/z*: 363 (M+1 for free base). Anal. Calcd for $C_{21}H_{22}N_4O_2 \cdot HCl \cdot 0.3H_2O$: C, 62.38; H, 5.88; N, 13.86; Cl, 8.77. Found: C, 62.31; H, 5.81; N, 13.60; Cl, 8.82.



Example 164



Example 165

Example 164 and Example 165

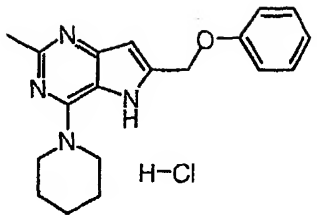
6-[(4-Fluorophenyl)methyl]-2-methyl-4-piperidylpyrrolo [3,2-*d*]pyrimidine Hydrochloride and 7-(4-Fluorophenyl)-2,6-dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride.

Using the method described in Example 30 by employing [2-(4-fluorophenyl)-1-methylvinyl]pyrrolidine (freshly prepared before use from (4-fluorophenyl) acetone (Aldrich Chemical Company), pyrrolidine and $TiCl_4$ (1.64 g, 8.00 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.66 g, 8.00 mmol), *N*,*N*-diisopropylethylamine (1.4 mL, 8.00 mmol), piperidine (1.3 mL, 12.8 mmol), NEt_3 (1.8 mL) and $SnCl_2$ (24 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 108 g (4%) of 6-[(4-fluorophenyl)methyl]-2-methyl-4-piperidylpyrrolo [3,2-*d*]pyrimidine as a white colored solid and 172 mg (7%) of 7-(4-fluorophenyl)-2,6-dimethyl-4-piperidyl pyrrolo[3,2-*d*]pyrimidine as a white colored solid.

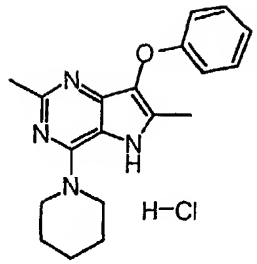
Example 164: 6-[(4-Fluorophenyl)methyl]-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (108 mg, 0.33 mmol)

was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.40 mL, 0.40 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum at 60 °C to give 97 mg (3%) of Example 164 as a white colored solid. Mp: 254-255 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.70 (br s, 6), 2.51 (s, 3), 3.98 (br s, 4), 6.21 (s, 1), 7.17 (t, 2, J = 8.9), 7.35 (dd, 2, J = 8.6, 8.5), 12.04 (s, 1), 13.90 (s, 1). MS m/z: 325 (M+1 for free base). Anal. Calcd for $C_{19}H_{21}FN_4$•HCl: C, 63.24; H, 6.15; N, 15.42; Cl, 9.93. Found: C, 63.26; H, 6.15; N, 15.42; Cl, 9.93.

Example 165: 7-(4-Fluorophenyl)-2,6-dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (162 mg, 0.50 mmol) was dissolved in 5:1 EtOAc/MeOH (15 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.50 mL, 0.50 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum at 60 °C to give 122 mg (5%) of Example 165 as a beige colored solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.63 (br s, 6), 2.37 (s, 3), 2.46 (s, 3), 3.95 (br s, 4), 7.30 (t, 2, J = 8.8), 7.40 (dd, 2, J = 8.5, 8.5), 12.10 (s, 1), 13.31 (s, 1). MS m/z: 325 (M+1 for free base). Anal. Calcd for $C_{19}H_{21}FN_4$•HCl: C, 63.24; H, 6.15; N, 15.53; Cl, 9.82. Found: C, 63.40; H, 6.22; N, 15.31; Cl, 9.94.



Example 166



Example 167

Example 166 and Example 167

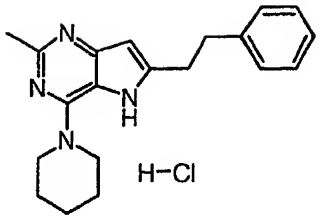
[(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl) methoxy]benzene hydrochloride and 2,6-Dimethyl-7-phenoxy-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing [2-pyrrolidinylprop-2-enyloxy]benzene and [2-pyrrolidinylprop-1-enyloxy]benzene (freshly prepared before use from phenoxy-2-propanone (Aldrich Chemical Company), pyrrolidine and $TiCl_4$ (2.03 g, 13.50 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.79 g, 13.50 mmol), *N,N*-diisopropylethylamine (2.4 mL, 13.5 mmol), piperidine (2.2 mL, 21.6 mmol), NEt_3 (3.0 mL) and $SnCl_2$ (40 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 110 mg (3%) of [(2-methyl-4-piperidyl pyrrolo[4,5-*d*]pyrimidin-6-yl)methoxy]benzene as a brown colored gummy solid and 60 mg (1%) of 2,6-dimethyl-7-phenoxy-4-piperidylpyrrolo[3,2-*d*]pyrimidine as a yellow colored solid.

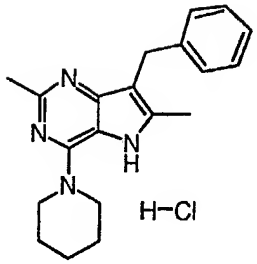
Example 166: [(2-Methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl)methoxy]benzene (107 mg, 0.33 mmol) was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to

boiling. To the hot solution was added 1 M ethereal HCl (0.40 mL, 0.40 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum at 60 °C to give 66 mg (2%) of Example 166 as a white colored solid. Mp: 238-239 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.64 (br s, 6), 2.48 (s, 3), 3.94 (br s, 4), 5.22 (s, 2), 6.66 (s, 1), 6.92 (t, 1, J = 7.3), 7.01 (d, 2, J = 7.9), 7.26 (dt, 2, J = 1.1, 7.4), 12.64 (s, 1), 14.18 (s, 1). MS m/z: 323 (M+1 for free base). Anal. Calcd for $C_{19}H_{22}N_4O$•HCl: C, 63.59; H, 6.46; N, 15.61; Cl, 9.88. Found: C, 63.48; H, 6.48; N, 15.51; Cl, 10.02.

Example 167: 2,6-Dimethyl-7-phenoxy-4-piperidyl pyrrolo[3,2-*d*]pyrimidine (57 mg, 0.18 mmol) was dissolved in 5:1 EtOAc/MeOH (6 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.20 mL, 0.20 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum at 60 °C to give 45 mg (1%) of Example 167 as a beige colored powder. Mp: >280 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.64 (br s, 6), 2.20 (s, 3), 2.43 (s, 3), 3.94 (br s, 4), 6.88 (d, 2, J = 8.3), 7.01 (t, 1, J = 7.0), 7.28 (t, 2, J = 7.4), 12.01 (s, 1), 13.84 (s, 1). MS m/z: 323 (M+1 for free base). Anal. Calcd for $C_{19}H_{22}N_4O$•HCl•0.75H_2O: C, 61.28; H, 6.63; N, 15.05; Cl, 9.52. Found: C, 61.25; H, 6.31; N, 14.73; Cl, 9.44.



Example 168



Example 169

Example 168 and Example 169

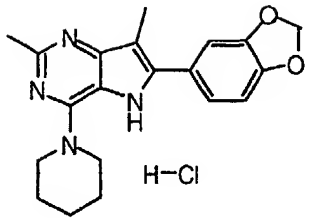
2-Methyl-6-(2-phenylethyl)-4-piperidylpyrrolo[3,2-*d*] pyrimidine Hydrochloride Hydrate and 2,6-Dimethyl-7-benzyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing [1-(2-phenylethyl)vinyl]pyrrolidine and [1-(3-phenylprop-1-enyl]pyrrolidine (freshly prepared before use from benzylacetone (Aldrich Chemical Company), pyrrolidine and $TiCl_4$ (2.23 g, 11.3 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.34 g, 11.3 mmol), *N,N*-diisopropylethylamine (2.0 mL, 11.3 mmol), piperidine (1.8 mL, 18.1 mmol), NEt_3 (2.5 mL) and $SnCl_2$ (34 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 500 mg (14%) of 2-methyl-6-(2-phenyl ethyl)-4-piperidylpyrrolo[3,2-*d*]pyrimidine as a brown colored solid and 181 mg (5%) of 2,6-dimethyl-7-benzyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine as a beige colored solid.

Example 168: 2-Methyl-6-(2-phenylethyl)-4-piperidylpyrrolo[3,2-*d*]pyrimidine (481 mg, 1.50 mmol) was dissolved in 5:1 EtOAc/MeOH (40 mL) and heated to

boiling. To the hot solution was added 1 M ethereal HCl (1.50 mL, 1.50 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum at 60 °C to give 271 mg (7%) of Example 168 as a beige colored powder. Mp: 236-238 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.60 (br s, 6), 2.45 (s, 3), 2.95 (t, 2, J = 8.4), 3.09 (t, 2, J = 8.4), 3.92 (br s, 4), 6.24 (s, 1), 7.11-7.14 (m, 1), 7.16-7.25 (m, 4), 11.88 (s, 1), 14.06 (s, 1). MS *m/z*: 321 (M+1 for free base). Anal. Calcd for $C_{20}H_{24}N_4 \cdot HCl \cdot 0.25H_2O$: C, 66.46; H, 7.11; N, 15.51; Cl, 9.81. Found: C, 66.40; H, 7.12; N, 15.37; Cl, 9.91.

Example 169: 2,6-Dimethyl-7-benzyl-4-piperidyl pyrrolo[3,2-*d*]pyrimidine (175 mg, 0.55 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.60 mL, 0.60 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum at 60 °C to give 71 mg (2%) of Example 169 as a beige colored powder. Mp: >240 °C (dec). ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.61 (br s, 6), 2.28 (s, 3), 2.52 (s, 3), 3.91 (br s, 4), 4.07 (s, 2), 7.08-7.13 (m, 3), 7.20 (t, 2, J = 7.6), 11.99 (s, 1), 14.21 (s, 1). MS *m/z*: 321 (M+1 for free base). Anal. Calcd for $C_{20}H_{24}N_4 \cdot HCl \cdot 0.4H_2O$: C, 65.97; H, 7.14; N, 15.39; Cl, 9.74. Found: C, 66.04; H, 6.98; N, 15.37; Cl, 9.79.



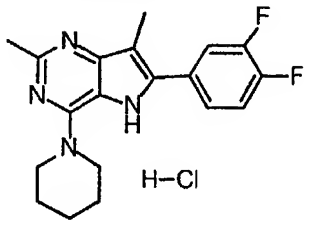
Example 170

5-[2,7-Dimethyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]-2*H*-benzo[*d*]1,3-dioxolane Hydrochloride Hydrate.

Using the method described in Example 30 by employing 5-(1-pyrrolidinylprop-1-enyl)-2*H*-benzo[*d*]1,3-dioxolene (freshly prepared before use from 3,4-methylenedioxypropiophenone (Lancaster Chemical Company), pyrrolidine and $TiCl_4$ (2.03 g, 8.78 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.82 g, 8.78 mmol), *N,N*-diisopropylethylamine (1.5 mL, 8.78 mmol), piperidine (1.4 mL, 14.1 mmol), NEt_3 (2.0 mL) and $SnCl_2$ (26 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3$/MeOH as eluant to give 247 mg (8%) of 5-[2,7-dimethyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]-2*H*-benzo[*d*]1,3-dioxolane as a beige colored solid. This compound (241 mg, 0.69 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.70 mL, 0.70 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 165 mg (5%) of the title compound as a beige colored powder. Mp: 268-269 °C. ^1H NMR (DMSO-d_6; 400 MHz): δ 1.63 (br s, 6), 2.24 (s, 3),

2.54 (s, 3), 3.96 (br s, 4), 6.07 (s, 2), 7.05-7.11 (m, 2), 7.05 (d, 1, J = 1.3), 11.76 (s, 1), 13.89 (s, 1). MS m/z: 351 (M+1 for free base). Anal. Calcd for $C_{20}H_{22}N_4O_2 \cdot HCl \cdot 0.4H_2O$: C, 60.95; H, 6.09; N, 14.22; Cl, 9.00. Found: C, 60.99; H, 5.88; N, 14.19; Cl, 9.09.

Example 171

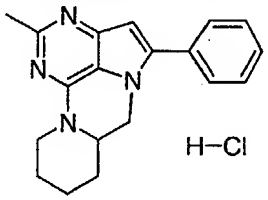


6-(3,4-Difluorophenyl)-2,7-dimethyl-4-piperidyl pyrrolo[3,2-*d*]pyrimidine Hydrochloride.

Using the method described in Example 30 by employing [1-(3,4-difluorophenyl)prop-1-enyl] pyrrolidine (freshly prepared before use from 3,4-difluoropropiophenone (Lancaster Chemical Company), pyrrolidine and $TiCl_4$ (2.27 g, 10.2 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.11 g, 10.2 mmol), *N,N*-diisopropylethylamine (1.8 mL, 10.2 mmol), piperidine (1.6 mL, 16.3 mmol), NEt_3 (2.3 mL) and $SnCl_2$ (31 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3$/MeOH as eluant to give 305 mg (9%) of 6-(3,4-difluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine as a brown colored oil. This compound (304 mg, 0.89 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.90 mL, 0.90 mmol). The solution was allowed to

cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 201 mg (5%) of the title compound as a beige colored powder. Mp: >280 °C. ^1H NMR (DMSO-d_6; 400 MHz): δ 1.63 (br s, 6), 2.27 (s, 3), 2.56 (s, 3), 3.98 (br s, 4), 7.47-7.49 (m, 1), 7.61 (q, 1, J = 8.6), 7.78 (dt, 1, J = 1.4, 7.8), 11.96 (s, 1), 14.08 (s, 1). MS m/z: 343 (M+1 for free base). Anal. Calcd for $C_{19}H_{20}F_2N_4 \bullet 1.1HCl$: C, 59.64; H, 5.56; N, 14.65; Cl, 10.22. Found: C, 59.59; H, 5.56; N, 14.67; Cl, 10.02.

Example 172

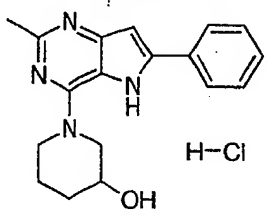


2-Methyl-5-phenyl-7,7a,8,9,10,11-hexahydro-1,3,11a-triaza-pyrrolo[3,2,1-de]phenanthridine Hydrochloride monohydrate.

A solution of 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-*d*]pyrimidine (1.0 g, 4.1 mmol, Example 1e) and 2-hydroxymethyl piperidine (Aldrich Chemical Company) (0.49 g, 4.2 mmol) in N-methyl morpholine (10 mL) was heated at 110 °C for 12 h. The solvent was concentrated *in vacuo* and the residue was mixed with $POCl_3$ (5 mL, 54 mmol) and toluene (20 mL). The mixture was heated at reflux for 6.5 h before it was concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (50 mL)-H_2O (50 mL) and the pH of the aqueous phase was adjusted to pH ~8 with NaOH solution (2 N). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x). The combinbed organic phase was dried over Na_2SO_4, concentrated *in vacuo*, and

the resulting residue was purified by flash chromatography on silica gel (MeOH in CH_2Cl_2, 1-15%). The free base was treated with ethereal HCl to give the title compound as the HCl salt (0.18 g, 14%). Mp: >280 °C. ^1H NMR (DMSO-d_6; 500 MHz): d 1.58-1.66 (m, 3), 1, 85-1.91 (m, 2), 2.05 (d, 1, J = 10), 2.55 (s, 3), 3.43 (t, 1, J = 10), 4.22-4.25 (m, 2), 4.77 (t, 1, J = 14), 4.86(d, 1, J = 13), 7.10 (s, 1), 7.49-7.57 (m, 3), 8.02 (d, 2, J = 8). MS m/z: 305 (M+1). Anal. Calcd for $C_{19}H_{20}N_4 \cdot 2HCl \cdot H_2O$: C, 57.72; H, 6.12; N, 14.18; Cl, 17.95. Found: C, 57.69; H, 6.24; N, 14.02; Cl, 17.79.

Example 173

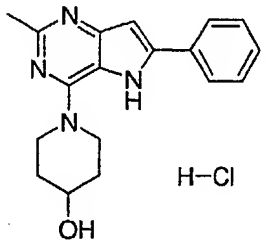


1-(2-Methyl-6-phenylpyrrollo[2,3-*e*]pyrimidine-4-yl)piperidin-3-ol Hydrochloride Hydrate.

A solution of 2-methyl-4-chloro-6-phenyl pyrrolo [3,2-*d*]pyrimidine (0.6 g, 2.5 mmol, Example 1e), 3-hydroxy piperidine hydrogen chloride (Aldrich Chemical Company) (0.34 g, 2.5 mmol), and *iso*-Pr_2NEt (1.0 mL) in toluene was heated at reflux for 24 h. The mixture was allowed to cool to room temperature and was treated with aqueous NaOH (0.5 N, 10 mL). The slurry was filtered, and the solid was washed with CH_2Cl_2 (3 x 5 mL). The solid was dissolved in a mixture of CH_2Cl_2 (5 mL) plus a minimum amount of MeOH and the solution was treated with HCl (2 mL, 1 N in ether). The resulting mixture was filtered and the solid was trituated with hot EtOAc to afford the title compound as a white solid (0.54 g, 71%). ^1H NMR (DMSO-d_6; 400 MHz): d 1.44-1.66 (m, 2), 1.74-1.80 (m, 2), 2.58 (s, 3), 3.76 (br s, 2),

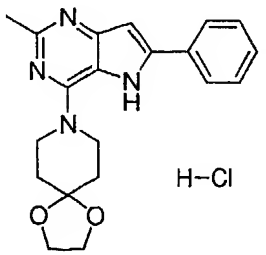
3.99 (br s, 1), 4.30 (d, br d, J = 12), 5.15 (br s, 0.5), 6.89 (s, 1), 7.44-7.57 (m, 3), 7.98 (d, 2, J = 7.2), 11.90-11.98 (br s, 1). MS m/z: 308 (M+1). Anal. Calcd for $C_{18}H_{20}N_4O \cdot 1.19HCl \cdot 0.34H_2O$: C, 60.38; H, 6.16; N, 15.65; Cl, 11.80. Found: C, 60.38; H, 5.91; N, 15.61; Cl, 11.83.

Example 174



1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidine-4-yl) piperidin-4-ol Hydrochloride Hydrate.

The title compound was prepared according to the procedure described in Example 173, using 4-hydroxy piperidine (Aldrich Chemical Company)(0.26 g, 2.57 mmol) and 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-d]pyrimidine (Example 1e) (0.49 g, 2.0 mmol), as a white solid (0.30 g, 48%). ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.51-1.59 (m, 2), 2.58 (s, 3), 3.78-3.90 (m, 3), 4.34-4.37 (m, 2), 6.89 (s, 1), 7.49-7.57 (m, 3), 7.96 (d, 2, J = 7.2), 11.8 (br s, 1). MS m/z: 308 (M+1). Anal. Calcd for $C_{18}H_{20}N_4O \cdot HCl \cdot 0.33H_2O$: C, 61.62; H, 5.94; N, 15.97; Cl, 10.10. Found: C, 61.62; H, 5.91; N, 15.81; Cl, 10.28.

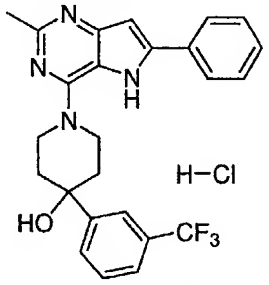


Example 175

8-Aza-8-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl)-1,4-dioxaspiro[4,5]decane Hydrochloride Hydrate.

The title compound was prepared according to the procedure described in Example 173, using 1,4-dioxa-8-azaspiro[4,5]decane (Aldrich Chemical Company)(0.35 g, 2.50 mmol) and 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-*d*]pyrimidine (Example 1e) (0.60 g, 2.47 mmol), as a white solid (0.46 g, 53%). ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.83 (br t, 4), 2.58 (s, 3), 3.97(s, 4), 4.12 (br t, 4), 6.93 (s, 1), 7.50-7.6 (m, 3), 7.96 (d, 2, J = 6.8), 12.0 (br s, 1). MS *m/z*: 350 (M+1). Anal. Calcd for $C_{20}H_{22}N_4O_2 \cdot 1.01HCl \cdot 0.3H_2O$: C, 61.18; H, 6.06; N, 14.27; Cl, 9.13. Found: C, 61.18; H, 5.76; N, 14.35; Cl, 9.36.

Example 176

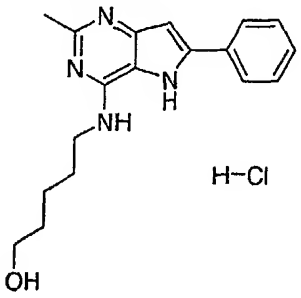


1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl)-4-[3-(trifluoromethyl)phenyl]piperidin-4-ol Hydrochloride Hydrate.

The title compound was prepared according to the procedure described in Example 173, using 4-[3-(trifluromethyl)phenyl]-4-piperidinol hydrochloride (Acros Organics) (0.6 g, 2.1 mmol) and 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-*d*]pyrimidine (Example 1e) (0.42 g, 1.73 mmol), as a white solid (0.5 g, 59%). ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.83 (d, 2, J = 13), 2.18 (t, 2, J = 11), 2.59 (s, 3), 3.73 (br s, 2) , 4.81 (br s, 2), 5.70 (s, 1), 6.93 (s, 1), 7.49-7.62 (m, 5),

7.83 (d, 1, J = 7.6), 7.89 (s, 1), 7.97 (d, 2, J = 7.6). MS m/z: 453 (M+1). Anal. Calcd for $C_{25}H_{23}F_3N_4O \cdot 1.17HCl \cdot 0.17H_2O$: C, 60.25; H, 4.96; N, 11.25; Cl, 8.33. Found: C, 60.25; H, 5.16; N, 10.88; Cl, 8.18.

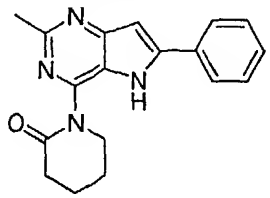
Example 177



5-[(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidine-4-yl) amino]pentan-1-ol Hydrochloride Hydrate.

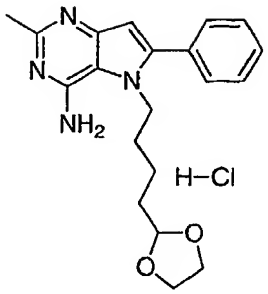
The title compound was prepared according to the procedure described in Example 173, using 5-amino-1-pentanol (Fluka Chemika) (0.35 g, 3.4 mmol) and 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-d]pyrimidine (Example 1e) (0.42 g, 1.73 mmol), as a white solid (0.36 g, 61%). ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.46 (br s, 4), 1.68 (bs, 2), 2.58 (s, 3), 3.62 (br s, 2) , 4.40 (br s, 1), 6.93 (s, 1), 7.46-7.54 (m, 3), 8.05 (br, 2), 9.61 (s, 1), 13.47 (s, 1). MS m/z: 311 (M+1). Anal. Calcd for $C_{18}H_{22}N_4O \cdot HCl \cdot 0.28H_2O$: C, 61.42; H, 6.75; N, 15.92; Cl, 10.07. Found: C, 61.42; H, 6.67; N, 15.75; Cl, 10.17.

Example 178



1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl) piperidin-2-one.

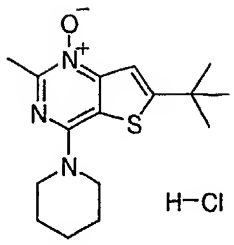
Phenyl-5-[(2-methyl-6-phenylpyrrolo[2,3-*e*] pyrimidine-4-yl)amino]pentanoate. A mixture of 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-*d*]pyrimidine (Example 1e) (1.0 g, 4.11 mmol), 5-aminovaleric acid (Aldrich Chemical Company) (0.78 g, 0.66 mmol), and phenol (1.0 g, 10.6 mmol) was heated at 150 °C for 24 h. The mixture was let cool to room temperature and was treated with 5 mL each of EtOAc and ether. The mixture was filtered and the solid was washed with ether (3x) to give a light yellow solid (1.15 g). A solution of this intermediate (0.2 g), EDCI-HCl (Aldrich Chemical Company)(0.32 g, 1.7 mmol), and a catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2/DMF/pyridine (5:2:2 mL) was stirred at room temperature overnight. EtOAc (50 mL) was added and the resulting mixture was washed with H_2O (3x). The combined aqueous phase was back extracted with ether (1x) and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel with 6% NH_3 (2N solution in MeOH) in CH_2Cl_2 to give the title compound as a white solid (0.018 g, 8%). ^1H NMR ($CDCl_3$; 400 MHz): d 1.96-2.13 (m, 4), 2.66Ð2.89 (m, 5), 4.17 (t, 2, J = 5.6), 6.86(d, 1, J = 2.0), 7.38Ð7.54 (m, 3), 7.74 (d, 2, J = 8.0), 9.68 (s, 1). MS *m/z*: 307 (M+1). HPLC (H_2O/CH_3CN, 50:50): Rf 1.444, >97% pure.



Example 179

5-(4-(1,3-Dioxolan-2-yl)butyl)-2-methyl-6-phenyl pyrrolo[3,2-*d*]pyrimidine-4-ylamine Hydrochloride.

A solution of 2-methyl-4-amino-6-phenyl pyrrolo [3,2-*d*]pyrimidine (Example 22) (0.079 g, 0.35 mmol), 2-(1-chlorobutyl)-1,3-dioxolane (Fluka Chemika) (0.14 g, 0.85 mmol), and *iso*-Pr_2NEt (0.3 mL, 1.7 mmol) in toluene/DMF (2.5:1.0 mL) was heated at reflux for 6 days. The mixture was allowed to cool to room temperature and purified by flash chromatography on silica gel with 5% NH_3 (2N in MeOH) 5% MeOH in CH_2Cl_2 to afford the product. The product was dissolved in CH_2Cl_2/EtOAc (1:1) and the solution was treated with a 2 M ethereal HCl (2 mL). The resulting slurry was filtered, and the solid was washed with hot EtOAc (3x) to give a yellow solid (29 mg, 23%). ^1H NMR (DMSO-d_6; 400 MHz): d 1.53 (m, 2), 1.64 (m, 2), 1.84 (m, 2), 2.68 (s, 3), 3.86 (m, 2) , 4.32 (br t, 2), 4.80 (t, 1), 7.34 (s, 1), 7.48-7.58 (m, 3), 8.11 (d, 2), 8.89 (s, 1), 9.17 (s, 1), 13.90 (s, 1). MS *m/z*: 353 (M+1). Anal. Calcd for $C_{20}H_{24}N_4O_2 \cdot 2HCl$: C, 56.47; H, 6.16; N, 13.18. Found: C, 56.36; H, 6.08; N, 13.21.

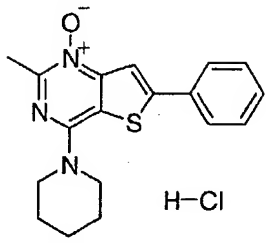


Example 180

6-(*tert*-Butyl)-2-methyl-4-piperidylthiopheno[3,2-*d*] pyrimidin-1-ol Hydrochloride.

A solution of 6-(*tert*-butyl)-2-methyl-4-piperidyl thiopheno[3,2-*d*]pyrimidine (Example 34) (0.207 g, 0.716 mmol) in CH_2Cl_2 (5 mL) was treated with *meta*-chloro perbenzoic acid (Aldrich Chemical Company) (0.5 g, 2.9 mmol, 57-86% pure) and the reaction mixture was stirred at room temperature for 3 days. The reaction mixture was treated with aqueous NaOH (0.5 N, 10 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x) and the combined organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica with MeOH in CH_2Cl_2 (0-10%) to give the product as a yellow solid (0.047 g, 21%). The product was dissolved in CH_2Cl_2 (1.0 mL) and the solution was treated with HCl (1 N in ether, 1.0 mL). The resulting solution was left capped at room temperature for 3 days whereby large yellow crystals were formed. The solvent was decanted and the crystals were washed with 1:1 EtOAc-hexanes (3x) to give the title compound (~15 mg). Mp: 202-203 °C (dec). ^1H NMR ($CDCl_3$; 400 MHz): d 1.47 (s, 9), 1, 80 (br s, 6), 2.85 (s, 3), 4.05 (br s, 4), 7.46 (s, 1), 13.89 (br s, 1). MS *m/z*: 306 (M+1). Anal. Calcd for $C_{16}H_{23}N_3OS \cdot HCl$: C, 56.2; H, 7.08; N, 12.29; S, 9.38. Found: C, 55.96; H, 6.99; N, 12.15; Cl, 15.51. The structure was confirmed by x-ray crystallography.

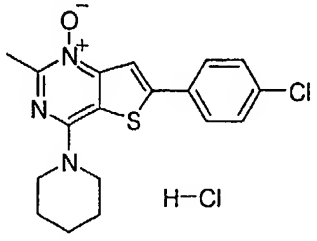
Example 181



2-Methyl-6-phenyl-4-piperidylthiopheno[3,2-*d*]pyrimidin-1-ol Hydrochloride

The oxidation was performed in a similar fashion as described in Example 180, using 240 mg (0.78 mmol) of 2-methyl-6-phenyl-4-piperidylthiopheno[3,2-*d*] pyrimidine (Example 32) and 240 mg (1.39 mmol, 57-86%) of *meta*-chloroperbenzoic acid to afford the product (76 mg, 30%). The product was dissolved in 2.0 mL of CH_2Cl_2 and the solution was treated with 0.3 mL of HCl (2N in ether). The solid was collected and was washed with hot EtOAc (3x) to give the title compound as a yellow solid (54 mg). ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.73 (s, 6), 2.69 (s, 3), 4.06 (br s, 4), 7.56 (br s, 3), 7.99 (br s, 2), 8.09 (s, 1). MS *m/z*: 326 (M+1).

Example 182

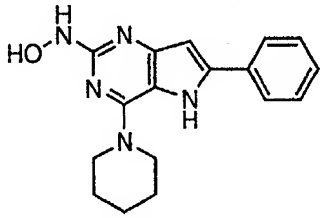


6-(4-Chloro-phenyl)-2-methyl-4-piperidylthiopheno[3,2-*d*]pyrimidin-1-ol Hydrochloride Hydrate.

The oxidation was performed in a similar fashion as described in Example 180, using 246 mg (0.72 mmol) of 6-(4-chloro-phenyl)-2-methyl-4-piperidylthiopheno [3,2-*d*]pyrimidine (Example 33) and 250 mg of *meta*-

chloroperbenzoic acid (1.45 mmol, 57-80%), to afford the product (156 mg, 60%). A total of 226 mg of the product were dissolved in 2.5 mL of CH_2Cl_2 and the solution was treated with 0.3 mL of HCl (2N in ether). The solid was collected and washed with hot EtOAc (3x) to give the title compound as a yellow solid (87 mg). ^1H NMR (DMSO-d_6; 400 MHz): d 1.73 (br s, 6), 2.69 (s, 3), 4.07 (br s, 4), 6.84 (s, 1), 763 (d, 2, J = 8.4), 8.01 (d, 2, J = 8.4), 8.15 (s, 1). MS m/z: 360, 362. Anal. Calcd for $C_{18}H_{18}N_3ClOS \cdot HCl \cdot 0.5H_2O$: C, 53.33; H, 4.97; N, 10.37; S, 7.71; Cl, 17.49. Found: C, 53.00; H, 4.77; N, 10.21; S, 7.70; Cl, 15.51.

Example 183

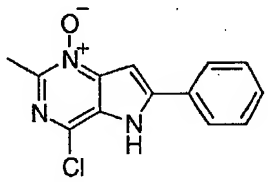


6-Phenyl-4-piperidyl)pyrrolo[3,2-d]pyrimidine-2-yl hydroxylamine Hydrochloride.

To a sealed 3-mL vial was 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (Example 203(c)) (59 mg, 0.189 mmol), hydroxylamine hydrochloride (Aldrich Chemical Company) (52.5 mg, 0.754 mmol) and pyridine (1.0 mL). The solution was heated at 100 °C for 4 h. The reaction mixture was allowed to cool to room temperature and pyridine was removed *in vacuo*. The resulting residue was washed with sat. $NaHCO_3$, and extracted with $CHCl_3$ three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography on silica gel with $MeOH/CH_2Cl_2/NH_4OH$(4:95:1) as eluant to afford 35 mg (60 %) of a light-brown solid. The free base (35 mg, 0.113

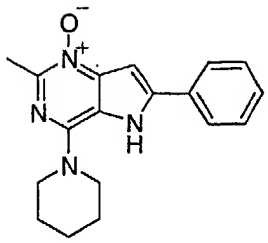
mmol) was dissolved in hot MeOH (2 mL) and anhydrous ethereal HCl (0.113 mL of a 2 M soln, 0.226 mmol) was added dropwise. The precipitate was collected by filtration, washed with EtOAc/ether (1:1) (3 x 0.5 mL) and dried over vacuum to give 25 mg (58 %) of the title compound as a light brown solid. ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.40-1.50 (m, 6), 3.70-3.80 (m, 4), 6.48 (s, 1), 7.30-7.80 (m, 5), 9.72 (s, 0.5), 10.50 (s, 0.5), 11.46 (s, 0.5), 12.44 (s, 0.5). MS *m/z* : 310 (M+1). Anal. Calcd for $C_{17}H_{19}N_5O \cdot 2HCl$: C, 53.41; H, 5.54; N, 18.32. Found: C, 54.37; H, 6.16; N, 17.86.

Example 184



(a) 4-Chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidin-1-ol.

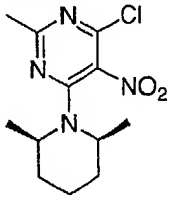
To a solution of 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-*d*]pyrimidine (Example 1e) (0.30 g, 1.23 mmol) in CH_2Cl_2 (5 mL) was added *meta*-chloroperbenzoic acid (Aldrich Chemical Company) (0.48 g, 2.79 mmol, 57-86%). The mixture was stirred at room temperature for 12 h whereby it was filtered. The solid was further washed with ether (3x) to afford the product as a yellow solid. ^{1}H NMR (MeOH-d_4; 400 MHz): d 2.60 (s, 3), 7.30 (s, 1), 7.47-7.56 (m, 3), 8.12 (d, 2, J = 7.4), 12.4-13.1 (br s, 1). MS *m/z*: 259 (M+1).



(b) 2-Methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*] pyrimidin-1-ol.

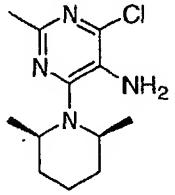
A solution of the chloride intermediate, prepared in Example 184(a), (0.178g, 0.69 mmol), and piperidine (0.50 mL, 5 mmol) in DMF (2.0 mL) was heated at 80 °C for 4 h. The solution was allowed to cool to room temperature and was diluted with EtOAc (~20 mL). The resulting mixture was washed with aqueous NaOH (0.5 M, 10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography on silica gel with NH_3 (2 N in MeOH)-MeOH in CH_2Cl_2 (0-5%), followed by preparative TLC with NH_3 (2 N in MeOH)-MeOH in CH_2Cl_2 (2.5-5%), give the product (43 mg, 20%), which was crystallized from MeOH/EtOAc (1:4) as light yellow plates. Mp: 169-170 °C; ^1H NMR (MeOH-d_4; 400 MHz): d 1.78 (s, 6), 2.65 (s, 3), 4.06 (br s, 4), 6.93 (s, 1), 7.32-7.54 (m, 3), 7.82 (d, 2, J = 10.8). MS *m/z*: 309 (M+1). The structure was determined to be the monohydrate by x-ray crystallography.

Example 185



(a) 4-((6*S*, 2*R*)-2,6-Dimethylpiperidyl)-6-chloro-2-methyl-5-nitropyrimidine.

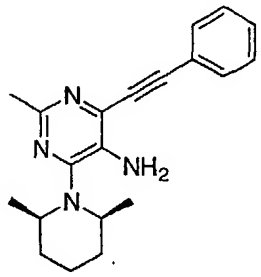
To a solution of 4,6-dichloro-2-methyl-5-nitro pyrimidine (Example 76 (b)) (2.44 g, 11.78 mmol, 1.0 eq) and triethylamine (Aldrich Chemical Company, 2.38 g, 23.56 mmol, 2.0 eq) in THF (12 mL) was added a solution of *cis*-2,6-dimethylpiperidine (Aldrich Chemical Company, 1.59 g, 11.78 mmol, 1.0 eq) in THF (12 mL) slowly. The final reaction mixture was stirred at room temperature for 3 days. After the removal of solvent *in vacuo*, the crude material was purified by flash chromatography on silica gel with 0-10% EtOAc/hexanes as eluant to afford the title compound (2.80 g, 84%) as a brown solid. ^{1}H NMR ($CDCl_3$, 500 MHz): d 1.29 (d, 6, J = 7.0), 1.56 (m, 1), 1.60-1.63 (m, 2), 1.73 (m, 2), 1.84-1.90 (m, 1), 2.50 (s, 3), 4.42 (m, 2). MS *m/z*: 285 (M+H), *m/z*: 283 (M-H).



(b) 4-((6*S*, 2*R*)-2,6-Dimethylpiperidyl)-6-chloro-2-methylpyrimidine-5-ylamine.

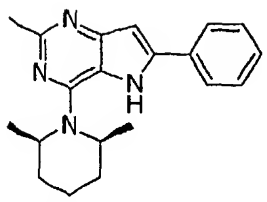
To a solution of 4-((6*S*, 2*R*)-2,6-dimethyl piperidyl)-6-chloro-2-methyl-5-nitropyrimidine (Example 185(a)) (2.26 g, 7.94 mmol, 1.0 eq) in anhydrous diethyl ether (15 mL) was added a freshly prepared solution of $SnCl_2 \cdot H_2O$ (Aldrich Chemical Company, 32 mL, 2.0 M in concentrated aqueous HCl) slowly under N_2 at 0 °C. The reaction mixture was stirred at room temperature for 3 h, and then was poured onto a ice bath containing NaOH (12 g). The aqueous phase was extracted with EtOAc (100 mL x 4). The water phase was passed through a pad of Celite® and was extracted again with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash

chromatography on silica gel with 0-50% EtOAc/hexanes as eluant to afford the title compound (795 mg, 40%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): d 0.75 (d, 6, *J* = 6.2), 1.31-1.34 (m, 2), 1.50-1.60 (m, 1), 1.72-1.76 (m, 3), 2.55 (s, 3), 3.03-3.07 (m, 2) 4.34 (br s, 2). MS *m/z*: 255 (M+H).



(c) 4-((6*S*, 2*R*)-2,6-Dimethylpiperidyl-2-methyl-6-(2-phenylethynyl)pyrimidine-5-ylamine.

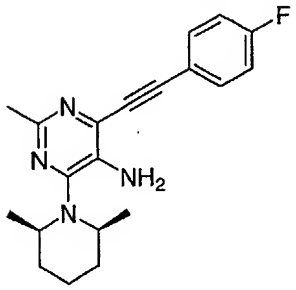
A mixture of 4-((6*S*, 2*R*)-2,6-dimethylpiperidyl)-6-chloro-2-methylpyrimidine-5-ylamine (Example 185(b)) (347 mg, 1.36 mmol, 1.0 eq), phenylacetylene (Aldrich Chemical Company, 279 mg, 2.73 mmol, 2.0 eq), $Pd(PPh_3)_2Cl_2$ (Aldrich Chemical Company, 48 mg, 0.068 mmol, 0.05 eq) and CuI (Aldrich Chemical Company, 13 mg, 0.068 mmol, 0.05 eq) in triethylamine (3 mL) was stirred under N_2 at 70 °C overnight. Upon cooling to room temperature, the reaction mixture was diluted with $CHCl_3$ (50 mL), passed through a pad of Celite® and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 0-8% EtOAc/hexanes as eluant to afford the title compound (412 mg, 95%) as a cherry colored semi-solid. ^{1}H NMR ($CDCl_3$, 400 MHz): d 0.78 (d, 6, *J* = 6.2), 1.25-1.40 (m, 2), 1.50-1.60 (m, 1), 1.74-1.77 (m, 3), 2.59 (s, 3), 4.57 (br s, 2), 7.38 (m, 3), 7.60 (m, 2). MS *m/z*: 321 (M+H).



(d) 4-((6*S*, 2*R*)-2,6-Dimethyl)-2-methyl-6-phenylpyrrolo [3,2-*d*]pyrimidine Hydrochloride:

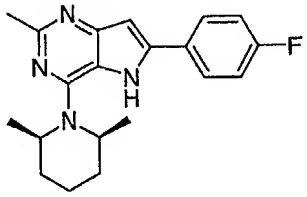
A solution of 4-((6*S*,2*R*)-2,6-dimethylpiperidyl-2-methyl-6-(2-phenylethynyl)pyrimidine-5-ylamine (Example 185(c)) (387 mg, 1.21 mmol)) and CuI (Aldrich Chemical Company, 21 mg, 0.121 mmol, 0.1 eq) in anhydrous DMF (3 mL) was stirred under N_2 at 110 °C overnight. Upon cooling to the room temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL), passed through a pad of Celite® and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel with 0–80% EtOAc/hexanes as eluant to afford the free base of the product as a brown solid (200 mg, 50%). Mp: 223-225 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): d 1.28 (d, 6, *J* = 6.8), 1.61–1.70 (m, 3), 1.81–1.96 (m, 3), 2.61 (s, 3), 4.63 (br s, 2), 6.78 (s, 1), 7.39 (t, 1, *J* = 7.3), 7.48 (t, 2, *J* = 7.3), 7.66 (d, 2, *J* = 7.3), 8.39 (s, 1). MS *m/z*: 321 (M+H). The above material (195 mg, 0.61 mmol, 1.0 eq) was dissolved in diethyl ether (20 mL) and HCl (0.64 ml of a 1.0 M soln in ether, 0.64 mmol, 1.05 eq) was added dropwise. After stirring at room temperature for 10 min, the solution was concentrated *in vacuo*. Recrystallization from MeOH afforded the title compound (127 mg, 65%) as an off-white solid. Mp: >270 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): d 1.34 (d, 6, *J* = 6.7), 1.59 (m, 1), 1.78 (m, 4), 1.94 (m, 1), 2.61 (s, 3), 14 (br s, 2), 6.88 (s, 1), 7.51-7.59 (m, 3), 7.95 (d, 2, *J* = 6.8), 11.60 (s, 1), 14.28 (s, 1). MS *m/z*: 321 (M+H). Anal. Calcd for $C_{20}H_{24}N_4$ ·HCl: C, 67.31; H, 7.06; N, 15.70. Found: C, 67.04; H, 6.97; N, 15.60.

Example 186



(a) 4-((6*S*, 2*R*)-2,6-Dimethylpiperidyl)-6-[2-(4-fluoro phenyl)ethynyl]-2-methylpyrimidine-5-ylamine.

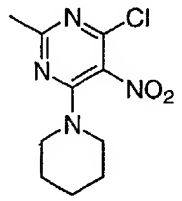
This compound was synthesized by the method described in Example 185(c) from 4-((6*S*, 2*R*)-2,6-dimethylpiperidyl)-6-chloro-2-methylpyrimidine-5-ylamine (Example 185(b)) (449 mg, 1.76 mmol, 1.0 eq) and 1-ethynyl-4-fluorobenzene (Aldrich Chemical Company, 500 mg, 4.16 mmol, 2.36 eq). The title compound was obtained as a brown solid (381 mg, 64%). Mp: 134-136 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): d 0.78 (d, 6, J = 6.2), 1.25-1.40 (m, 2), 1.50-1.60 (m, 1), 1.70-1.80 (m, 3), 2.59 (s, 3), 3.05-3.15 (m, 2), 4.55 (br s, 2), 7.05-7.09 (m, 2), 7.57-7.60 (m, 2). MS *m/z*: 339 (M+H).



(b) 4-((6*S*, 2*R*)-2,6-Dimethylpiperidyl)-6-(4-fluorophenyl)-2-methylpyrrolo[3,2-*d*]pyridine Hydrochloride Monohydrate.

This compound was synthesized by the method described in Example 185(d) from 4-((6*S*,2*R*)-2,6-dimethylpiperidyl)-6-[2-(4-fluorophenyl)ethynyl]-2-methylpyrimidine-5-ylamine (Example 186(a)) (335 mg, 0.99 mmol, 1.0 eq). The free base of the product was obtained as a brown solid (175 mg, 53%). Mp: 210-203

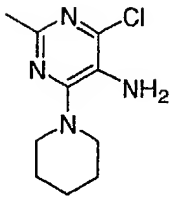
°C. ^{1}H NMR ($CDCl_3$, 400 MHz): d 1.27 (d, 6, J = 6.8), 1.66-1.69 (m, 3), 1.81-1.96 (m, 3), 2.61 (s, 3), 4.61 (br s, 2), 6.71 (s, 1), 7.17 (t, 1, J = 8.5), 7.63 (dd, 2, J = 5.2, 8.5), 8.32 (s, 1). MS *m/z*: 339 (M+H). The above material (175 mg, 0.52 mmol, 1.0 eq) was used to prepare HCl salt by the method described in 185(d) to 86 mg (49%) of the title compound as a brown solid. Mp: >275 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): d 1.34 (d, 6, J = 6.7), 1.59 (m, 1), 1.78 (m, 4), 1.94 (m, 1), 2.61 (s, 3), 14 (br s, 2), 6.88 (s, 1), 7.51-7.59 (m, 3), 7.95 (d, 2, J = 6.8), 11.60 (s, 1), 14.28 (s, 1). MS *m/z*: 339 (M+H), *m/z*: 337 (M-H). Anal. Calcd for $C_{20}H_{23}FN_4 \cdot HCl \cdot H_2O$: C, 61.14; H, 6.67; N, 14.26. Found: C, 61.05; H, 6.78; N, 14.18.



Example 187

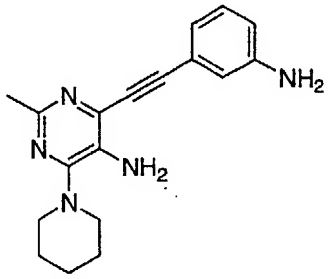
(a) 6-Chloro-2-methyl-5-nitro-4-piperidylpyrimidine.

To a solution of 4,6-dichloro-2-methyl-5-nitro pyrimidine (Example 76(b)) (8.00 g, 38.6 mmol, 1.00 eq) in THF (60 mL) was added a solution of piperidine (Aldrich Chemical Company, 3.29 g, 38.6 mmol, 1.00 eq) and diisopropylethylamine (Aldrich Chemical Company, 5.09 g, 39.4 mmol, 1.02 eq) dropwise through a additional funnel under N_2 at room temperature for 3 days. Diisopropylethylamine hydrogen chloride was filtered away as white solid, and the organic layer was concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 0-8% EtOAc/hexanes as eluant to afford the title compound (8.63 g, 87%) as a yellow solid. Mp: 62-64 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): d 1.67 (m,6), 2.50 (s,3), 2.53 (m,4).



(b) 6-Chloro-2-methyl-4-piperidylpyrimidine-5-ylamine.

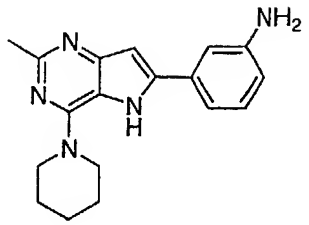
A solution of 6-chloro-2-methyl-5-nitro-4-piperidylpyrimidine (4.06 g, 15.8 mmol, 1.0 eq) in MeOH (68 mL) was hydrogenated in the presence of PtO_2 (Aldrich Chemical Company, 179 mg, 0.79 mmol, 0.05 eq)under H_2 (60 psi) at room temperature for 5 h. The reaction mixture was passed through a pad of Celite® and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 0-15% EtOAc/hexanes as eluant to afford the title compound (1.86 g, 52%) as a orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz): d 1.67 (m, 6), 2.48 (s, 3), 3.25 (m, 4), 3.67 (br s, 2). MS *m/z*: 227 (M+H).



(c) 6-[2-(3-Aminophenyl)ethynyl]-2-methyl-4-piperidylpyrimidine-5-ylamine.

This compound was synthesized by the method described in example 1(c) from 6-chloro-2-methyl-4-piperidylpyrimidine-5-ylamine (Example 187(b)) (1.42 g, 6.26 mmol, 1.0 eq) and 3-ethylnylaniline (TCI America, 1.47 g, 12.5 mmol, 2.0 eq). The title compound was obtained as a red solid (625 mg, 33%). ^{1}H NMR ($CDCl_3$, 400 MHz): d 1.69 (m, 6), 2.52 (s, 3), 3.27 (m, 4), 3.71 (s, 2), 3.92 (s, 2), 6.70 (d, 1, J =

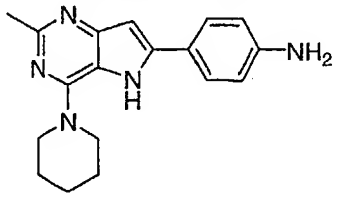
7.8), 6.90 (s, 1), 6.99 (d, 1, J = 7.8) 7.14 (t, 1, J = 7.8). MS m/z: 308 (M+H).



(d) 3-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenylamine Hydrochloride Monohydrate.

This compound was synthesized by the method described in Example 185(d) from 6-[2-(3-aminophenyl) ethynyl]-2-methyl-4-piperidylpyrimidine-5-ylamine (Example 187(c)) (492 mg, 1.6 mmol, 1.0 eq). The free base of the product was obtained as an off-white solid (202 mg, 34%). ^{1}H NMR (DMSO-d_6, 400 MHz): d 1.64 (br s, 6), 2.41 (s, 3), 3.72 9br s, 4), 5.21 (br s, 2), 6.53 (s, 1), 6.60 (d, 1, J = 7.6), 7.00 (m, 2), 7.12 (t, 1, J = 7.6), 10.97 (s, 1). MS m/z: 308 (M+H), m/z: 306 (M-H). The above material (202 mg, 0.66 mmol, 1.0 eq) was used to prepare HCl salt by the method described in Example 185(d) to give 80 mg (35%) of the title compound as a brown solid . Mp: >275 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): d 1.70 (m, 6), 2.56 (s, 3), 4.04 (m, 4), 5.41 (br s, 2), 6.71 (m, 2), 7.03 (m, 2), 7.19 (m, 1), 11.95 (s, 1), 14.25 (s, 1). MS m/z: 308 (M+H), m/z: 306 (M-H). Anal. Calcd for $C_{18}H_{21}N_5 \cdot HCl \cdot H_2O$: C, 59.74; H, 6.69; N, 19.36. Found: C, 59.79; H, 6.58; N, 19.34.

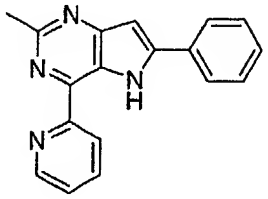
Example 188



4-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl] phenylamine Hydrochloride.

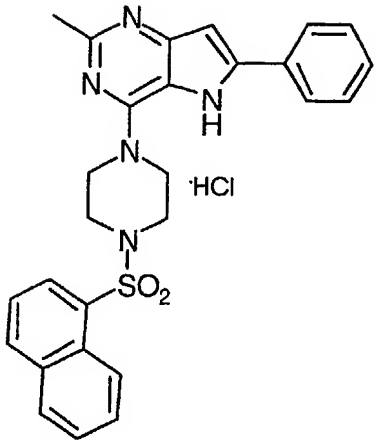
A solution of 6-chloro-2-methyl-4-piperidyl pyrimidine-5-ylamine (Example 187(a)) (1.36 g, 6.0 mmol, 1.0 eq), $Pd_2(PPh_3)_2Cl_2$ (Aldrich Chemical Company, 210 mmg, 0.30 mmol, 0.05 eq), Cu(I)I (Aldrich Chemical Company, 57 mg, 0.30 mmol, 0.05 eq) in triethylamine (10 mL) was deoxygenated by bubbling N_2 for 10 min, and was heated to 70 °C. A solution of 4-ethynylaniline (Lavastre, O; Cabioch, S.; Dixneuf, P. H. and Vohlidal, J. *Tetrahedron*, 1997, 53, 7595. 1.05 g, 9.0 mmol, 1.5 eq) in triethylamine (10 ml) deoxygenated by bubbling N_2 was transferred through a canula needle slowly. The final reaction mixture was stirred under N_2 at 70 °C for 48 h. Upon cooling to the room temperature, the reaction was diluted with CH_2Cl_2 (20 mL) and MeOH (20 mL), passed through a pad of Celite® and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 10% DMF-0.5% Triethylamine-Toluene as eluant to afford the free base of the product (370 mg, 20%) as an orange solid. Mp: 239-242 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): d 1.63 (br s, 6), 2.39 (s, 3), 3.65 (br s, 4), 5.42 (s, 2), 6.46 (s, 1), 6.46 (s, 1), 6.64 (d, 2, J = 8.5), 7.56 (d, 2, J = 8.5), 10.65 (s, 1). MS *m/z*: 308 (M+H). The above material (107 mg, 0.35 mmol, 1.0 eq) was used to prepare HCl salt by the method described in 1 (d) to give 47 mg (40%) of the title compound as a brown solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): d 1.68 (m, 6), 2.54 (s, 3), 4.00 (m, 4), 5.70 (br s, 2), 6.63 (s, 1), 6.67 (d, 2, J = 8.5), 7.64 (d, 2, J = 8.5), 11.55 (s, 1), 13.97 (s, 1). MS *m/z*: 308 (M+H), *m/z*: 306 (M-H). Anal. Calcd for $C_{18}H_{21}N_5 \cdot HCl$: C, 62.87; H, 6.45; Cl, 10.31 ; N, 20.37. Found: C, 62.66; H, 6.35; Cl, 10.56 ; N, 20.17.

Example 189



2-Methyl-6-phenyl-4-(2-pyridyl)pyrrolo[3,2-*d*] pyrimidine.

A mixture of 4-chloro-2-methyl-6-phenylpyrrolo [3,2-*d*]pyridine (150 mg, 0.61 mmol), 2-Pyridinyl tributylstannane (Maybridge, 270 mg, 0.73 mmol, 1.2 eq), *tris*(dibenzylideneacetone)dipalladium (0) (Aldrich Chemical Company, 14 mg, 0.015 mmol, 0.025 eq) and triphenylphosphine (Aldrich Chemical Company, 32 mg, 0.12 mmol, 0.2 eq) in anhydrous toluene was refluxed under N_2 for 48 h. Upon cooling to the room temperature, the reaction mixture was quenched with 5% HCl (30 mL), then neutralized with Na_2CO_3. The crude product was extracted with $CHCl_3$ (60 mL x 3), washed with water (150 mL x 1), saturated NaCl (150 mL x 1), dried with Na_2SO_4 and concentrated *in vacuo*. Chromatography (silica gel, 0-0.5% MeOH/CH_2Cl_2) afforded 155 mg (yellow solid, 89%). Mp: 182-183 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): d 2.90 (s, 3), 6.92 (d, 1, *J* = 2.4), 7.4-7.5 (m, 2), 7.55 (t, 2, *J* = 7.3), 7.67 (m, 1), 7.84 (d, 2, *J* = 7.3), 7.94 (t, 1, *J* = 7.9), 8.77 (d, 1, *J* = 7.9), 8.82 (d, 1, *J* = 4.2), 10. 96 (s, 1). MS *m/z*: 287 (M+1), 285 (M-1).



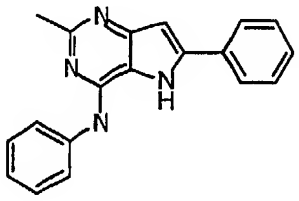
Example 190

1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)-4-naphthylsulfonyl) piperazine Hydrochloride Hydrate.

To an oven-dried, 50 ml round-bottomed flask was added 2-methyl-6-phenyl-4-piperazinylpyrrolo[3,2-*d*] pyrimidine (Example 26) (250 mg, 0.85 mmol), 1-naphthalenesulfonyl chloride (Aldrich Chemical Company) (232 mg, 1.02 mmol) and CH_2Cl_2 (25 ml). The slurry was stirred at room temperature under an N_2 as triethylamine (142 mL, 1.02 mmol) was added dropwise over 2 min. After 6 h the reaction was washed with saturated $NaHCO_3$ (3 x 20 ml) and then the aqueous layers were back extracted with CH_2Cl_2 (3 x 10 ml). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo* to leave a solid. The white solid was dried under vacuum overnight to give 391 mg (95%) of the free base of the title compound. The free base (391 mg, 0.80 mmol) was dissolved in a mixture of hot CH_2Cl_2/EtOAc (20ml) and anhydrous ethereal HCl (0.80 mL of a 1 M soln, 0.80 mmol) was added dropwise forming a precipitate immediately. After stirring at room temperature for 12 h the solution was filtered, solids collected, and dried in a vacuum oven at 60 °C overnight to give a quantitative yield of the title compound as light

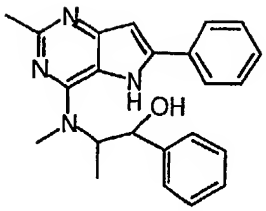
yellow solid. Mp: 195 °C (dec). ^{1}H NMR (DMSO-d_6; 400 MHz): d 2.53 (s, 4), 4.11 (t, 4, J = 4.7), 6.89 (s, 1), 7.53 (m, 3), 7.71 (m, 3), 7.94 (dd, 2, J = 6.6, J = 1.4), 8.11 (d, 1, J = 8.0), 8.20 (dd, 1, J = 6.6, J = 0.6), 8.31 (d, 1, J = 8.2), 8.72 (d, 1, J = 8.6), 12.03 (s, 1). MS m/z: 484.5 (M+1). Anal. Calcd for $C_{27}H_{25}N_5O_2S \cdot HCl \cdot 2H_2O$: C, 58.53; H, 5.09; N, 12.64; Cl, 6.40. Found: C, 58.45; H, 5.28; N, 12.49; Cl, 6.51.

Example 191



(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl) phenylamine Hydrochloride.

To a 5-mL, wheaton vial were added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (Example 1(e)) (100 mg, 0.41 mmol) and aniline (Aldrich Chemical Company) (0.37 mL, 4.1 mmol), followed by EtOH (1.5 mL). The reaction was heated at reflux for 4 h. The reaction mixture was allowed to cool to room temperature and the precipitate was collected by filtration, washed with hexanes, dried in a vacuum oven overnight to give 114 mg of a brown solid. The material was recrystallized from EtOH to give 57 mg (41%) of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6; 400 MHz): d 2.67 (s, 3), 7.04 (s, 1), 7.21-7.23 (m, 1), 7.44-7.59 (m, 5), 8.03 (d, 2, J = 8.0), 8.15 (d, 2, J = 8.0), 11.61 (br s, 1), 13.84 (br s, 1). MS m/z: 301 (M+1).

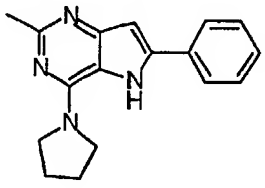


Example 192

2-[Methyl(2-methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)amino]-1-phenylpropan-1-ol.

To a 5-mL, Wheaton vial were added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (Example 1(e)) (100 mg, 0.41 mmol) and ephedrine hydrochloride (Aldrich Chemical Company) (410 mg, 2.1 mmol), followed by addition of a solution of potassium carbonate (0.71 g, 5.1 mmol) in water (2.5 mL). The reaction mixture was stirred at 120 °C for 20 h, allowed to cool to room temperature and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* to give a brown residue, which was purified by flash chromatography on silica gel with 1:1 EtOAc/hexanes as eluant to give 23 mg (15%) of the title compound as a tan solid. ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.21 (d, 3, *J* = 6.8), 2.42 (s, 3), 3.21 (s, 3), 4.91 (m, 1), 5.02 (m, 1), 5.87 (br s, 1), 6.69 (s, 1), 7.18-7.85 (m, 10), 10.73 (br s, 1). MS *m/z*: 373 (M+1), 371 (M-1).

Example 193

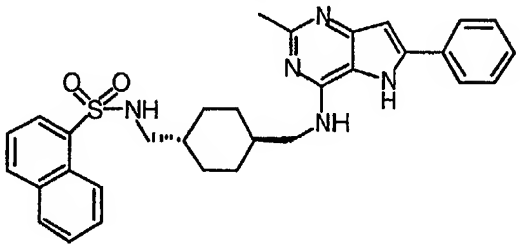


2-Methyl-6-phenyl-4-pyrrolidinylpyrrolo[3,2-*d*] pyrimidine Hydrochloride Monohydrate.

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (Example 1(e)) (500

mg, 2.1 mmol), pyrrolidine (Aldrich Chemical Company) (0.86 mL, 10.3 mmol), and K_2CO_3 (2.83 g, 20.5 mmol) in H_2O (10 mL) to give 0.722 g of the free base as an off-white solid. To a solution of the above material in $CHCl_3$ (10 mL) and MeOH (0.5 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (2.0 mL, 2.0 mmol). After stirring the reaction at room temperature for 40 min, the precipitate formed was collected by filtration, recrystallized in MeOH/H_2O to give 0.37 g (57%) of the title compound as off-white crystals. Mp: >296 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.99-2.08 (m, 4), 2.57 (s, 3), 3.81 (m, 2), 4.18 (m, 2), 6.88 (s, 1), 7.49-7.57 (m, 3), 7.96 (d, 2, J = 6.9), 11.62 (br s, 1). MS m/z: 279 (M+1). Anal. Calcd for $C_{17}H_{18}N_4 \cdot HCl \cdot H_2O$: C, 61.35; H, 6.36; N, 16.83; Cl, 10.65. Found: C, 61.55; H, 6.49; N, 16.75; Cl, 10.56.

Example 194

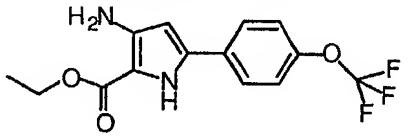


***trans*-[(4-{[(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)amino]methyl}cyclohexyl)methyl](naphthylsulfonyl) amine Hydrochloride Hydrate.**

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (Example 1(e)) (300 mg, 1.2 mmol), trans-{[4-(aminomethyl)cyclohexyl] methyl}(naphthylsulfonyl)amine (Rueger, H. et al WO 97/20823) (2.0 g, 6.1 mmol), and K_2CO_3 (1.7 g, 12.3 mmol) in H_2O (8 mL). The residue was purified by flash chromatography on silica gel with 100:5 $CHCl_3$/MeOH as

eluant to give 473 mg (71%) of the free base as an off-white solid. To a solution of the above material in MeOH (5 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.9 mL, 0.9 mmol). After stirring the reaction at room temperature for 30 min, the precipitate formed was collected by filtration, recrystallized in MeOH/H_2O to give 0.19 g of the title compound as off-white crystals. Mp: 165-170 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 0.71-0.88 (m, 4), 1.25 (m, 1), 1.53 (m, 1), 1.63-1.66 (m, 2), 1.76-1.78 (m, 2), 2.57 (s, 3), 2.63 (m, 2), 3.46 (m, 2), 6.93 (s, 1), 7.47-8.22 (m, 12), 8.68 (br s, 1), 9.28 (br s, 1), 13.23 (br s, 1), 14.04 (br s, 1). MS *m/z*: 540 (M+1). Anal. Calcd for $C_{31}H_{33}N_5O_2S \cdot HCl \cdot 2H_2O$: C, 60.82; H, 6.26; N, 11.44; Cl, 5.79; S, 5.24. Found: C, 60.73; H, 6.16; N, 11.35; Cl, 5.91; S, 5.16.

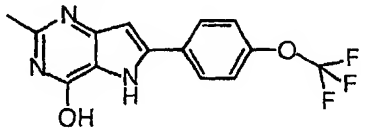
Example 195



(a) Ethyl 3-amino-5-[4-(trifluoromethoxy)phenyl] pyrrole-2-carboxylate.

To a 250-mL, round-bottomed flask were added 4-trifluoromethoxybenzoyl acetonitrile (5.00 g, 21.8 mmol), *p*-toluenesulfonic anhydride (8.55 g, 26.2 mmol) and CH_2Cl_2 (100 mL). To the above solution was then added Et_3N (4.6 mL, 32.7 mmol) dropwise. After 16 h of stirring at ambient temperature, the reaction mixture was partitioned between H_2O and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give an orange solid. Sodium ethoxide was prepared freshly from Na° (1.76 g, 76.3 mmol) and absolute ethanol (50

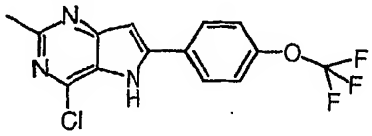
mL) in an oven-dried, 250-mL, round-bottomed flask equipped with a positive flow of N_2 gas. To the above solution was then added a solution of the crude orange solid and diethyl aminomalonate hydrochloride (5.54 g, 26.2 mmol) in ethanol (85 mL) and THF (7 mL) dropwise through an addition funnel. After the addition was completed, the reaction mixture was stirred at ambient temperature for 3 h and concentrated *in vacuo*. Water and EtOAc were added, and the aqueous layer was back extracted with EtOAc (3x). The combined EtOAc layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a dark-red solid. This material was purified by flash chromatography on silica gel with 1:9 EtOAc/hexanes as eluant to give 2.58 g (38%) of the title compound as an off-white solid. Mp: 175.0-178.0 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) d 1.30 (t, 3H, J = 7.0), 4.24 (q, 2H, J = 7.0), 5.12 (br s, 2H), 6.04 (d, 1H, J = 2.3), 7.35 (d, 2H, J = 8.6), 7.88 (d, 2H, J = 8.6), 10.86 (br s, 1H); MS *m/z:* 314 (M+1); IR (Nujol, cm^{-1}): 3446, 3313, 1669; Anal. Calcd for $C_{14}H_{13}F_3N_2O_3$: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.24; H, 4.28; N, 8.81.



(b) 2-Methyl-6-[4-(trifluoromethoxy)phenyl]pyrrolo[3,2-*d*]pyrimidin-4-ol.

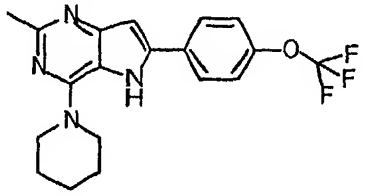
This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-[4-(trifluoromethoxy)phenyl]pyrrole-2-carboxylate (Example 195(a)) (2.24 g, 7.1 mmol), dry HCl gas in acetonitrile (60 mL) and then 6% aqueous sodium hydroxide (30 mL) and ethanol (50 mL) to give 1.68 g (76%) of the title compound as off-white solid. ^{1}H NMR (DMSO-d_6; 500 MHz): d 2.31 (s, 3), 6.81 (s, 1), 7.43

(d, 2, J = 8.6), 8.05 (d, 2, J = 8.6), 11.81 (br s, 1), 12.36 (br s, 1). MS m/z: 310 (M+1), 308 (M-1).



(c) [4-(4-Chloro-2-methylpyrrolo[4,5-*d*]pyrimidin-6-yl) phenoxy]trifluoromethane.

This compound was prepared according to the method described in Example 68 (b) by employing 2-methyl-6-[4-(trifluoromethoxy)phenyl]pyrrolo[3,2-*d*]pyrimidin-4-ol (Example 195(b)) (1.67 g, 5.4 mmol) and $POCl_3$ (12.6 mL, 135 mmol) to give 1.32 g (75%) of the title compound as brown solid. ^1H NMR ($CDCl_3$; 500 MHz): d 2.80 (s, 3), 6.93 (s, 1), 7.38 (d, 2, J = 8.5), 7.80 (d, 2, J = 8.5). MS m/z: 328, 330 (M+1); 326, 328 (M-1).

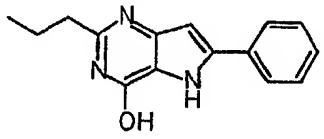


(d) Trifluoro[4-(2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl)phenoxy]methane Hydrochloride Monohydrate.

This compound was prepared according to the method described in Example 2 by employing [4-(4-chloro-2-methylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenoxy]trifluoro methane (Example 195(c)) (650 mg, 2.0 mmol), piperidine (Aldrich Chemical Company) (1.0 mL, 9.9 mmol), and K_2CO_3 (2.7 g, 20 mmol) in H_2O (15 mL) to give 351 mg (47%) of the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.0 mL, 1.0 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH/H_2O to give 0.156 g

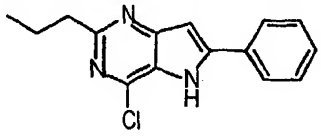
of the title compound as off-white crystals. ^{1}H NMR (DMSO-d_6; 500 MHz): d 1.70-1.72 (m, 6), 2.57 (s, 3), 4.06-4.07 (m, 4), 6.93 (s, 1), 7.56 (d, 2, J = 8.6), 8.13 (d, 2, J = 8.6), 12.01 (br s, 1), 14.21 (br s, 1). MS m/z: 377 (M+1). Anal. Calcd for $C_{19}H_{19}F_3N_4O \cdot HCl \cdot H_2O$: C, 52.97; H, 5.15; N, 13.00; Cl, 8.23. Found: C, 53.01; H, 5.13; N, 12.90; Cl, 8.34.

Example 196



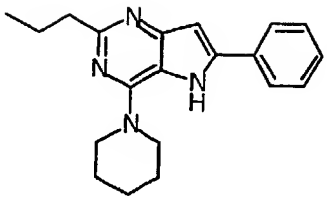
(a) 6-Phenyl-2-propylpyrrolo[3,2-*d*]pyrimidin-4-ol.

This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-phenylpyrrole-2-carboxylate (Example 66(b)) (2.05 g, 8.9 mmol), dry HCl gas in butyronitrile (70 mL) and then 6% aqueous sodium hydroxide (30 mL) and ethanol (50 mL) to give 2.12 g (94%) of the title compound as a gray solid. ^{1}H NMR (DMSO-d_6; 400 MHz): d 0.92 (t, 3, J = 7.4), 1.67-1.77 (m, 2), 2.55 (t, 2, J = 7.4), 6.80 (s, 1), 7.32-7.46 (m, 3), 7.93 (d, 2, J = 7.6), 11.77 (br s, 1), 12.29 (br s, 1). MS m/z: 254 (M+1).



(b) 4-Chloro-6-phenyl-2-propylpyrrolo[3,2-*d*]pyrimidine.

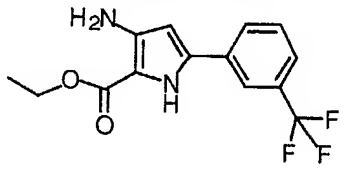
This compound was prepared according to the method described in Example 68 (b) by employing 6-phenyl-2-propylpyrrolo[3,2-*d*]pyrimidin-4-ol (Example 196(a)) (2.12 g, 8.4 mmol) and $POCl_3$ (15.7 mL, 168 mmol) to give 1.46 g (64%) of the title compound as a tan solid. ^{1}H NMR ($CDCl_3$; 500 MHz): d 1.01 (t, 3, J = 7.4), 1.85-1.94 (m, 2), 2.99 (t, 2, J = 7.7), 6.95 (s, 1), 7.45-7.53 (m, 3), 7.76 (d, 2, J = 7.9), 8.95 (br s, 1).



(c) 6-Phenyl-4-piperidyl-2-propylpyrrolo[3,2-*d*] pyrimidine Hydrochloride Monohydrate.

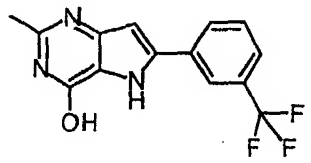
This compound was prepared according to the method described in Example 2 by employing 4-chloro-6-phenyl-2-propylpyrrolo[3,2-*d*]pyrimidine (Example 196 (b)) (500 mg, 1.8 mmol), piperidine (Aldrich Chemical Company) (0.91 mL, 9.2 mmol), and K_2CO_3 (2.54 g, 18 mmol) in H_2O (15 mL) to give 534 mg (91%) of the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.7 mL, 1.7 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH/H_2O to give 0.324 g of the title compound as off-white crystals. Mp: 258.0-262.5 °C. ^1H NMR (DMSO-d_6; 400 MHz): d 0.92 (t, 3, J = 7.4), 1.67 (m, 6), 1.72-1.81 (m, 2), 2.77 (t, 2, J = 7.4), 4.02-4.03 (m, 4), 6.86 (s, 1), 7.45-7.53 (m, 3), 7.91 (d, 2, J = 7.0), 12.00 (br s, 1). MS *m/z*: 321 (M+1). Anal. Calcd for $C_{20}H_{24}N_4 \cdot HCl \cdot H_2O$: C, 64.07; H, 7.26; N, 14.96; Cl, 9.46. Found: C, 64.16; H, 7.31; N, 15.01; Cl, 9.57.

Example 197



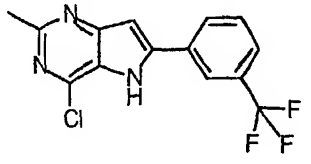
(a) Ethyl 3-amino-5-[3-(trifluoromethyl)phenyl] pyrrole-2-carboxylate.

This compound (5.22 g, 37%) was prepared according to the method described in Example 195(a) by employing 3-trifluoromethylbenzoyl acetonitrile (10 g, 46.9 mmol) and was recrystallized from toluene. Mp: 181.5-182.0 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) d 1.31 (t, 3H, J = 7.0), 4.25 (q, 2H, J = 7.0), 5.12 (br s, 2H), 6.15 (d, 1H, J = 2.6), 7.58 (d, 2H, J = 8.1), 8.00-8.01 (m, 1H), 8.22 (s, 1H), 11.06 (br s, 1H); MS *m/z:* 298 (M+1); IR (Nujol, cm^{-1}): 3441, 3356, 1641; Anal. Calcd for $C_{14}H_{13}F_3N_2O_2$: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.10; H, 4.48; N, 9.14.



(b) 2-Methyl-6-[3-(trifluoromethyl)phenyl]pyrrolo[3,2-*d*]pyrimidin-4-ol.

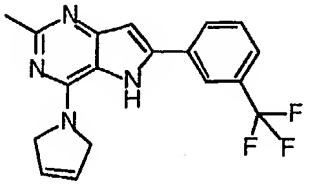
This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-[3-(trifluoromethyl)phenyl]pyrrole-2-carboxylate (Example 197(a)) (5.05 g, 17.0 mmol), dry HCl gas in acetonitrile (120 mL) and then 6% aqueous sodium hydroxide (70 mL) and ethanol (120 mL) to give 2.82 g (57%) of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6; 500 MHz): d 2.32 (s, 3), 6.94 (s, 1), 7.65-7.67 (m, 2), 8.21-8.22 (m, 1), 8.37 (s, 1), 11.83 (br s, 1), 12.50 (br s, 1). MS *m/z*: 294 (M+1).



(c) 4-Chloro-2-methyl-6-[3-(trifluoromethyl)phenyl] pyrrolo[3,2-*d*]pyrimidine.

This compound was prepared according to the method described in Example 68 (b) by employing 2-methyl-6-[3-(trifluoromethyl)phenyl]pyrrolo[3,2-*d*]pyrimidin-4-ol

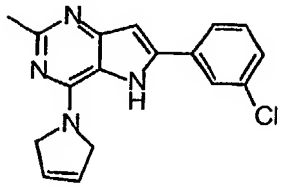
(Example 197(b)) (2.82 g, 9.6 mmol) and $POCl_3$ (18 mL, 192 mmol) to give 1.33 g (45%) of the title compound as a tan solid. ^1H NMR ($CDCl_3$; 400 MHz): d 2.79 (s, 3), 6.99 (s, 1), 7.63-7.73 (m, 2), 8.14 (d, 1, J = 7.6), 8.40 (s, 1).



(d) 2-Methyl-4-(3-pyrrolinyl)-6-[3-(trifluoromethyl) phenyl]pyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate.

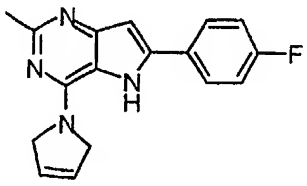
This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-[3-(trifluoromethyl)phenyl]pyrrolo[3,2-*d*]pyrimidine (Example 197(c)) (400 mg, 1.3 mmol), 3-pyrroline (Aldrich Chemical Company) (0.49 mL, 6.4 mmol), and K_2CO_3 (1.78 g, 12.8 mmol) in H_2O (10 mL) to give 422 mg (96%) of the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.3 mL, 1.3 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH/H_2O to give 0.226 g of the title compound as off-white crystals. Mp: >270 °C. ^1H NMR (DMSO-d_6; 400 MHz): d 2.61 (s, 3), 4.61 (m, 2), 5.06 (m, 2), 6.16 (d, 2, J = 18), 7.11 (s, 1), 7.79-7.83 (m, 1), 7.89 (d, 1, J = 7.9), 8.29 (d, 1, J = 7.9), 8.35 (s, 1), 11.74 (br s, 1). MS *m/z*: 345 (M+1). Anal. Calcd for $C_{18}H_{17}F_3N_4 \cdot HCl \cdot H_2O$: C, 54.21; H, 4.55; N, 14.05; Cl, 8.89. Found: C, 54.21; H, 4.39; N, 13.80; Cl, 8.75.

Example 198



6-(3-Chlorophenyl)-2-methyl-4-(3-pyrrolinyl)pyrrolo [3,2-*d*]pyrimidine Hydrochloride Hydrate.

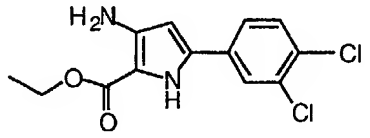
This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-(3-chlorophenyl)pyrrolo[3,2-*d*]pyrimidine (Example (70(d)) (474 mg, 1.7 mmol), 3-pyrroline (Aldrich Chemical Company) (0.65 mL, 8.5 mmol), and K_2CO_3 (2.35 g, 17 mmol) in H_2O (10 mL) to give the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.7 mL, 1.7 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH/H_2O to give 0.317 g (54%) of the title compound as off-white crystals. Mp: 287.5-293.0 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 2.60 (s, 3), 4.60 (m, 2), 5.06 (m, 2), 6.14 (d, 2, J = 14), 7.04 (s, 1), 7.57-7.60 (m, 2), 7.95-7.98 (m, 1), 8.13 (s, 1), 11.64 (br s, 1). MS *m/z*: 311 (M+1). Anal. Calcd for $C_{17}H_{15}ClN_4 \cdot HCl \cdot 1.25H_2O$: C, 55.24; H, 4.04; N, 15.16; Cl, 19.18. Found: C, 55.24; H, 4.92; N, 15.02; Cl, 18.98.



Example 199

6-(4-Fluorophenyl)-2-methyl-4-(3-pyrrolinyl)pyrrolo [3,2-*d*]pyrimidine Hydrochloride Hydrate.

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-(4-fluorophenyl)pyrrolo[3,2-*d*]pyrimidine (example 73(c)) (413 mg, 1.6 mmol), 3-pyrroline (Aldrich Chemical Company) (0.61 mL, 7.9 mmol), and K_2CO_3 2.18 g, 15.8 mmol) in H_2O (10 mL) to give the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.6 mL, 1.6 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH/H_2O to give 0.334 g (64%) of the title compound as tan crystals. ^{1}H NMR (DMSO-d_6; 400 MHz): d 2.60 (s, 3), 4.58 (m, 2), 5.05 (m, 2), 6.13 (d, 2, *J* = 12), 6.92 (s, 1), 7.37-7.44 (m, 2), 8.03-8.09 (m, 2), 11.65 (br s, 1). MS *m/z*: 295 (M+1). Anal. Calcd for $C_{17}H_{15}FN_4 \cdot HCl \cdot 1.25H_2O$: C, 57.82; H, 5.27; N, 15.87; Cl, 10.04. Found: C, 57.82; H, 5.29; N, 15.71; Cl, 9.94.

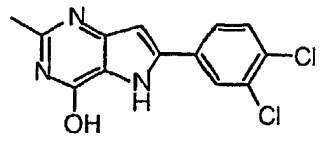


Example 200

(a) Ethyl 3-amino-5-(3,4-dichlorophenyl)pyrrole-2-carboxylate.

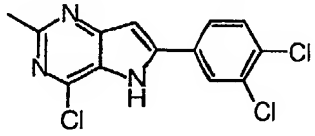
The title compound (2.43 g, 31%) was prepared according to the method described in Example 195(a) by employing 3,4-dichlorobenzoyl acetonitrile (5.57 g, 26.0 mmol) and was recrystallized from toluene. Mp: 184.0-185.0 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) d 1.30 (t, 3H, *J* = 7.0), 4.24 (q, 2H, *J* = 7.0), 5.12 (br s, 2H), 6.11 (s, 1H), 7.60 (d, 1H, *J* = 8.5), 7.72 (d, 1H, *J* = 8.5), 8.14 (s, 1H), 10.95 (br s, 1H); MS *m/z*: 299 (M+1); IR (Nujol, cm^{-1}): 3440, 3337, 1638; Anal. Calcd

for $C_{13}H_{12}Cl_2N_2O_2$: C, 52.19; H, 4.04; N, 9.36; Cl, 23.70. Found: C, 52.20; H, 4.12; N, 9.23; Cl, 23.53.



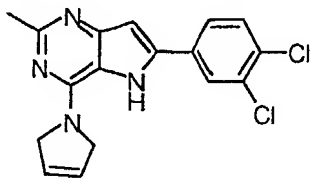
(b) 6-(3,4-Dichlorophenyl)-2-methylpyrrolo[3,2-*d*] pyrimidin-4-ol.

This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-(3,4-dichlorophenyl)pyrrole-2-carboxylate (Example 200(a)) (2.35 g, 7.9 mmol), dry HCl gas in acetonitrile (60 mL) and then 6% aqueous sodium hydroxide (35 mL) and ethanol (60 mL) to give 2.25 g (97%) of the title compound as a tan solid. ^{1}H NMR (DMSO-d_6; 500 MHz): d 2.31 (s, 3), 6.91 (s, 1), 7.69 (d, 1, J = 8.4), 7.91-7.93 (m,1), 8.27 (s,1), 11.84 (br s,1), 12.50 (br s,1).



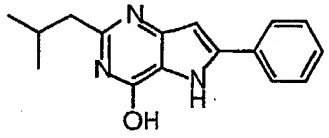
(c) 6-(3,4-Dichlorophenyl)-4-chloro-2-methylpyrrolo [3,2-*d*]pyrimidine.

This compound was prepared according to the method described in Example 68 (b) by employing 6-(3,4-dichlorophenyl)-2-methylpyrrolo[3,2-*d*]pyrimidin-4-ol (Example 200(b)) (2.25 g, 7.7 mmol) and $POCl_3$ (18 mL, 191 mmol) to give 1.07 g (45%) of the title compound as a tan solid. ^{1}H NMR ($CDCl_3$; 400 MHz): d 2.80 (s, 3), 6.93 (s, 1), 7.58 (m, 2), 7.84 (s, 1), 8.71 (br s, 1).



(d) 6-(3,4-Dichlorophenyl)-2-methyl-4-(3-pyrrolinyl) pyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate.

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-(3,4-dichlorophenyl)pyrrolo[3,2-*d*]pyrimidine (Example 200(c)) (400 mg, 1.3 mmol), 3-pyrroline (Aldrich Chemical Company) (0.49 mL, 6.4 mmol), and K_2CO_3 (1.77 g, 13 mmol) in H_2O (10 mL) to give 381 mg (86%) of the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.1 mL, 1.1 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH to give 0.121 g of the title compound as tan crystals. ^{1}H NMR (DMSO-d_6; 400 MHz): d 2.37 (s, 3), 4.37 (m, 2), 4.82 (m, 2), 5.92 (d, 2, *J* = 17), 6.85 (s, 1), 7.62 (d, 1, *J* = 8.5), 7.77-7.79 (m, 1), 8.12 (s, 1), 11.40 (br s, 1). MS *m/z*: 346 (M+1). Anal. Calcd for $C_{17}H_{14}Cl_2N_4 \cdot HCl \cdot 1.75H_2O$: C, 49.39; H, 4.52; N, 13.56; Cl, 25.76. Found: C, 49.39; H, 4.41; N, 13.46; Cl, 25.84.

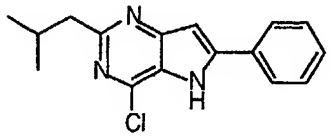


Example 201

(a) 2-(2-Methylpropyl)-6-phenylpyrrolo[3,2-*d*]pyrimidin-4-ol.

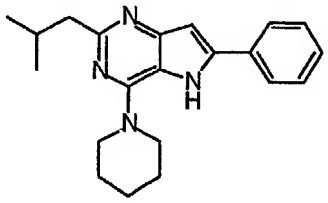
This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-phenylpyrrole-2-carboxylate ((Example 66(b)) (2.50 g, 10.9 mmol), dry HCl gas in isovaleronitrile (50 g) and then 6% aqueous sodium hydroxide (35 mL) and ethanol (50 mL) to give 1.77 g (61%) of the title compound as a brown solid. ^{1}H NMR (DMSO-d_6; 500 MHz): d 0.92 (d, 6, *J* = 7.0), 2.13-2.16 (m, 1), 2.44 (d, 2, *J* = 7.0), 6.79

(s,1), 7.32-7.49 (m 3), 7.93 (d, 2, J = 7.8), 11.74 (br s,1), 12.28 (br s,1). MS m/z: 268 (M+1), 266 (M-1).



(b) 4-Chloro-2-(2-methylpropyl)-6-phenylpyrrolo[3,2-*d*] pyrimidine.

This compound was prepared according to the method described in Example 68 (b) by employing 2-(2-methyl propyl)-6-phenylpyrrolo[3,2-*d*]pyrimidin-4-ol (Example 201(a)) (1.77 g, 6.6 mmol) and $POCl_3$ (15.5 mL, 165 mmol) to give 0.59 g (31%) of the title compound as a tan solid. ^1H NMR ($CDCl_3$; 500 MHz): d 0.99 (d, 6, J = 6.2), 2.34 (m, 1), 2.93 (d, 2, J = 6.2), 6.99 (s, 1), 7.27-7.42 (m 3), 7.80 (m, 2).

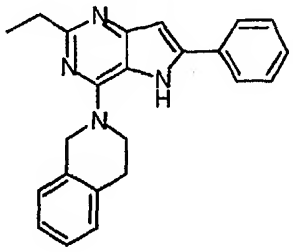


(c) 2-(2-Methylpropyl)-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate.

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-(2-methylpropyl)-6-phenylpyrrolo[3,2-*d*]pyrimidine (Example 201(b)) (588 mg, 2.1 mmol), piperidine (Aldrich Chemical Company) (1.0 mL, 10.3 mmol), and K_2CO_3 (2.85 g, 21 mmol) in H_2O (15 mL) to give the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (2.0 mL, 2.0 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH/H_2O to give 0.313 g (40%) of the title compound as orange crystals. Mp: 226.0-229.5

°C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.19 (d, 6, J = 7.0), 1.93 (m, 6), 2.40-2.50 (m, 1), 2.92 (d, 2, J = 7.0), 4.28-4.30 (m, 4), 7.13 (s, 1), 7.72-7.81 (m, 3), 8.18 (d, 2, J = 8.3), 12.25 (br s, 1). MS *m/z*: 335.5 (M+1). Anal. Calcd for $C_{21}H_{26}N_4 \cdot HCl \cdot H_2O$: C, 64.85; H, 7.52; N, 14.41. Found: C, 65.12; H, 7.32; N, 14.18.

Example 202

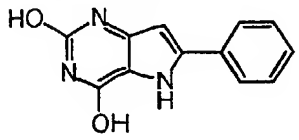


2-Ethyl-6-phenyl-4-(2-1,2,3,4-tetrahydroisoquinolyl) pyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate.

This compound was prepared according to the method described in Example 2 by employing 2-ethyl-4-chloro-6-phenylpyrrolo[3,2-*d*]pyrimidine (example (68b)) (500 mg, 1.7 mmol), 1,2,3,4-tetrahydroisoquinoline (Aldrich Chemical Company) (1.1 mL, 8.5 mmol), and K_2CO_3 (2.35 g, 17 mmol) in H_2O (15 mL) to give 410 mg (68%) of the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.2 mL, 1.2 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH/H_2O to give 0.42 g of the title compound as tan crystals. Mp: 170.0-171.5 °C. ^{1}H NMR (DMSO-d_6; 500 MHz): d 1.36 (t, 3, J = 7.5), 2.91 (t, 2, J = 7.5), 3.08 (t, 2, J = 5.8), 4.32 (t, 2, J = 5.8), 5.29 (s, 2), 6.92 (s, 1), 7.27-7.41 (m, 4), 7.53-7.60 (m, 3), 8.00 (d, 2, J = 7.3), 11.97 (br s, 1), 14.42 (br s, 1). MS *m/z*: 355.5 (M+1). Anal. Calcd

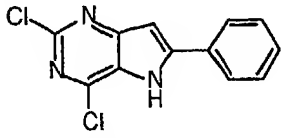
for $C_{23}H_{22}N_4 \cdot HCl \cdot H_2O$: C, 67.56; H, 6.16; N, 13.70. Found: C, 67.27; H, 6.10; N, 13.47.

Example 203



(a) 6-Phenylpyrrolo[3,2-*d*]pyrimidine-2,4-diol.

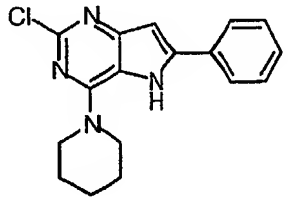
In a 1-l round-bottomed flask was added ethyl 3-amino-5-phenylpyrrole-2-carboxylate (Example 66 (b)) (20 g, 87 mmol), followed by acetic acid (435 mL) and H_2O (44 mL). Potassium cyanate (21.2 g, 261 mmol) dissolved in 70 mL of H_2O was then added dropwise through an addition funnel. The reaction mixture was stirred at room temperature for 15 h. The precipitate formed was collected by filtration, washed with H_2O and ether, dried to give a white solid. To the above solid in a 1-L round-bottomed flask was added 6% aqueous sodium hydroxide (435 mL). The suspension was heated at reflux for 2 h. The reaction mixture was acidified using 12 N HCl to pH 6. The precipitate formed was filtered, washed with H_2O, dried in a vacuum oven overnight to give 15.2 g (77%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6; 500 MHz): d 6.29 (s,1), 7.33-7.43 (m,3), 7.85 (d,2, J = 7.3), 10.62 (br s, 1), 10.85 (br s, 1), 12.19 (br s,1). MS m/z: 226 (M-1).



(b) 2,4-Dichloro-6-phenylpyrrolo[3,2-*d*]pyrimidine.

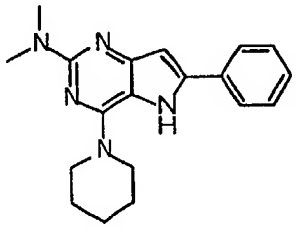
A mixture of 6-phenylpyrrolo[3,2-*d*]pyrimidine-2,4-diol (Example 203(a)) (6.0 g, 26.6 mmol) and $POCl_3$ (210 mL, 229 mmol) in a 500-mL, round-bottomed flask was heated at 120 °C for 60 h. $POCl_3$ was removed *in vacuo* to give a dark-red residue. Ice-water was added, and

the pH of the reaction mixture was adjusted to pH 6 by the addition of aqueous NH_3 at 0 °C. The resulting mixture was extracted three times with EtOAc. Combined organic layer were washed with brine, dried over Na_2SO_4, concentrated *in vacuo* and dried in a vacuum oven overnight to give 2.84 g (40%) of the title compound as an orange solid. ^{1}H NMR (DMSO-d_6; 400 MHz): d 6.95 (s, 1), 7.50-7.66 (m,3), 7.77 (d,2,*J*=8.1), 8.88 (br s,1).



(c) 2-Chloro-6-phenyl-4-piperidylpyrrolo[3,2-*d*] pyrimidine.

This compound was prepared according to the method described in Example 2 by employing 2,4-dichloro-6-phenylpyrrolo[3, 2-*d*]pyrimidine (Example 203(b)) (2.84 g, 10.8 mmol), piperidine (Aldrich Chemical Company) (5.3 mL, 53.8 mmol), and K_2CO_3 (14.9 g, 108 mmol) in H_2O (100 mL) to give 3.23 g (96%) of the title compound as an orange solid. ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.77 (m, 6), 3.83 (m, 4), 6.75 (s, 1), 7.37-7.55 (m, 3), 7.64 (d, 2, *J* = 7.3), 8.21 (br s, 1). MS *m/z*: 313, 315 (M+1); 311, 313 (M-1).

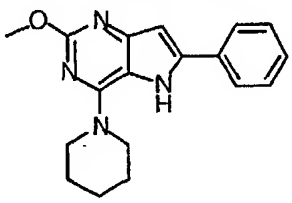


(d) Dimethyl(6-phenyl-4-piperidylpyrrolo[3,2-*d*] pyrimidin-2-yl)amine Hydrochloride Hydrate.

A mixture of 2-chloro-6-phenyl-4-piperidylpyrrolo [3,2-*d*]pyrimidine (Example 203(c)) (313 mg, 1 mmol), aqueous dimethylamine (Aldrich Chemical Company) (40

wt. %, 1.5 mL, 12 mmol), 5 mL of *n*-butanol and 0.2 mL of 12 N HCl in a 25-mL, round-bottomed flask was heated at reflux for 32 h under a stream of N_2. After cooling to room temperature, the precipitate was collected by filtration, washed with hexanes and dried in a vacuum oven overnight to give 239 mg (74%) of the title compound as orange crystals. Mp: >300 °C. ^{1}H NMR (DMSO-d_6; 500 MHz): d 1.68 (m, 6), 3.19 (s, 6), 3.95 (m, 4), 6.70 (s, 1), 7.45-7.54 (m, 3), 7.86 (d, 2, J = 7.4), 11.58 (br s, 1), 12.22 (br s, 1). MS *m/z*: 322.5 (M+1). Anal. Calcd for $C_{19}H_{23}N_5 \cdot 1.2HCl \cdot 1.75H_2O$: C, 57.68; H, 7.04; N, 17.71; Cl, 10.61. Found: C, 57.68; H, 6.99; N, 17.77; Cl, 10.85.

Example 204

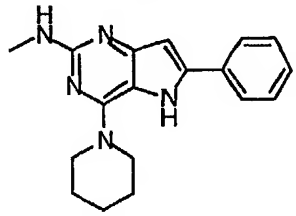


2-Methoxy-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate.

A mixture of 2-chloro-6-phenyl-4-piperidylpyrrolo [3,2-*d*]pyrimidine (Example 203(c)) (626 mg, 2 mmol), sodium methoxide (Aldrich Chemical Company) (25 wt. %, 0.78 mL, 4.5 mmol) and 2 mL of DMSO in a 15-mL, round-bottomed flask was heated at reflux for 72 h under a stream of N_2. After cooling to room temperature, the residue was partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layers were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica gel with 1:5 to 1:2 EtOAc/hexanes as eluant to give 217 mg (35%) of the free base as a purple solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.75

mL, 0.75 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH/H_2O to give 0.117 g of the title compound as a light-green crystals. Mp: 270–276 °C. ^{1}H NMR (DMSO-d_6; 500 MHz): d 1.73 (m, 6), 4.05 (m, 7), 6.75 (s, 1), 7.48–7.56 (m, 3), 7.92 (d, 2, J = 8.3), 11.87 (br s, 1), 13.87 (br s, 1). MS *m/z*: 309 (M+1). Anal. Calcd for $C_{18}H_{20}N_4O \cdot HCl \cdot H_2O$: C, 59.58; H, 6.39; N, 15.44; Cl, 9.77. Found: C, 59.59; H, 6.49; N, 15.47; Cl, 9.90.

Example 205

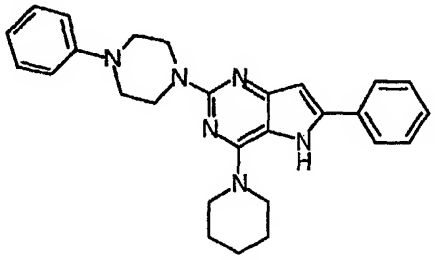


Methyl(6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-2-yl)amine Hydrochloride Monohydrate.

A mixture of 2-chloro-6-phenyl-4-piperidylpyrrolo [3,2-*d*]pyrimidine (Example 203(c)) (626 mg, 2 mmol), aqueous methylamine (Aldrich Chemical Company) (40 wt. %, 3.1 mL, 35 mmol), 10 mL of *n*-butanol and 0.4 mL of 12 N HCl in a 25-mL, round-bottomed flask was heated at reflux for 48 h under a stream of N_2. After cooling to room temperature, the solvent was evaporated *in vacuo* and the residue was partitioned between 5% $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layers were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica gel with 100:2 to 100:5 $CHCl_3$/MeOH as eluant to give 30 mg (5%) of the free base. ^{1}H NMR (DMSO-d_6; 500 MHz): d 1.68 (m, 6), 3.19 (s, 6), 3.95 (m, 4), 6.70 (s, 1), 7.45–7.54 (m, 3), 7.86 (d, 2, J = 7.4), 11.58 (br s, 1), 12.22 (br s, 1).

To a solution of the above material in $CHCl_3$ (5 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.1 mL, 0.1 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in $MeOH/H_2O$ to give 15 mg of the title compound as orange crystals. Mp: 195-200 °C. MS *m/z*: 308.5 (M+1). Anal. Calcd for $C_{19}H_{21}N_5 \cdot HCl \cdot H_2O$: C, 59.74; H, 6.68; N, 19.35. Found: C, 59.34; H, 6.69; N, 18.93.

Example 206

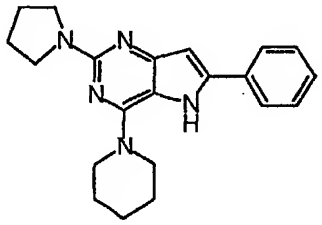


6-Phenyl-2-(4-phenylpiperazinyl)-4-piperidylpyrrolo [3,2-*d*]pyrimidine Hydrochloride Hydrate.

To the mixture of 2-chloro-6-phenyl-4-piperidyl pyrrolo[3,2-*d*]pyrimidine (Example 203(c)) (200 mg, 0.64 mmol) and 1-phenylpiperazine (Aldrich Chemical Company) (0.49 mL, 3.2 mmol) in a 50-mL, round-bottomed flask was added a solution of K_2CO_3 (0.89 g, 6.4 mmol) in 10 mL of H_2O. The reaction mixture was heated at reflux for 72 h under a stream of N_2. After cooling to room temperature, the mixture was partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layers were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica gel with 1:5 to 1:4 EtOAc/hexanes as eluant to give 107 mg (38%) of the free base as white solids. To a solution of the above material in $CHCl_3$ (5 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.24 mL, 0.24 mmol). After

stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the foam obtained was recrystallized in MeOH/H_2O to give 54 mg of the title compound as off-white solids. Mp: 267.5-270.0 °C. MS *m/z*: 439.5 (M+1). ^{1}H NMR (DMSO-d_6; 500 MHz): d 1.88 (m, 6), 4.07-4.15 (m, 12), 6.89 (s, 1), 7.00-7.02 (m, 2), 7.19 (d, 2, *J* = 8.0), 7.42-7.45 (m, 2), 7.63-7.72 (m, 3), 8.05 (d, 2, *J* = 7.6), 11.81 (br s, 1), 12.73 (br s, 1). Anal. Calcd for $C_{28}H_{32}N_6 \cdot 1.5HCl \cdot 1.25H_2O$: C, 62.82; H, 6.63; N, 16.28; Cl, 10.51. Found: C, 62.82; H, 6.68; N, 16.26; Cl, 10.63.

Example 207

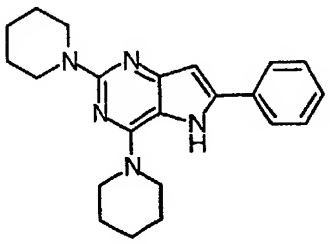


6-Phenyl-4-piperidyl-2-pyrrolidinylpyrrolo[3,2-*d*] pyrimidine Hydrochloride Monohydrate.

To the solution of 2-chloro-6-phenyl-4-piperidyl pyrrolo[3,2-*d*]pyrimidine (Example 203(c)) (250 mg, 0.80 mmol) in 2 mL of dioxane in a 5-mL, Wheaton vial was added pyrrolidine (0.33 mL, 4.0 mmol). The vial was capped and heated at 110 °C for 44 h. After cooling to room temperature, the precipitate was collected by filtration, washed with hexanes and dried in air to give 225 mg (81%) of the free base as light-yellow solids. To a solution of the above material in $CHCl_3$ (5 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.63 mL, 0.63 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the foam obtained was recrystallized in MeOH/H_2O to give 100 mg of the title compound as light-yellow crystals. Mp: >272 °C. ^{1}H NMR

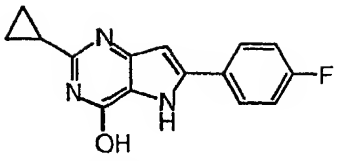
(DMSO-d_6; 400 MHz): d 1.68-1.70 (m, 6), 2.00 (m, 4), 3.57 (m, 4), 3.96-3.97 (m, 4), 6.67 (s, 1), 7.46-7.56 (m, 3), 7.88 (d, 2, J = 8.5), 11.57 (br s, 1), 12.11 (br s, 1). Anal. Calcd for $C_{21}H_{25}N_5 \cdot HCl \cdot H_2O$: C, 62.75; H, 7.02; N, 17.42; Cl, 8.82. Found: C, 62.85; H, 6.93; N, 17.36; Cl, 8.70.

Example 208



6-Phenyl-2,4-dipiperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride.

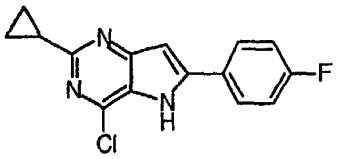
This compound was prepared according to the method described in Example 207 by employing 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (Example 203(c)) (250 mg, 0.8 mmol), piperidine (Aldrich Chemical Company) (0.39 mL, 4.0 mmol) and dioxane (2 mL) to give 198 mg (69%) of the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.54 mL, 0.54 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in $MeOH/H_2O$ to give 38 mg of the title compound as light-yellow crystals. Mp: >272 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.61-1.70 (m, 6), 3.74 (m, 4), 3.94 (m, 4), 6.71 (s, 1), 7.45-7.55 (m, 3), 7.87 (d, 2, J = 7.3), 11.61 (br s, 1), 12.44 (br s, 1). Anal. Calcd for $C_{22}H_{27}N_5 \cdot HCl$: C, 66.40; H, 7.09; N, 17.60; Cl, 8.91. Found: C, 66.25; H, 7.21; N, 17.48; Cl, 9.03.



Example 209

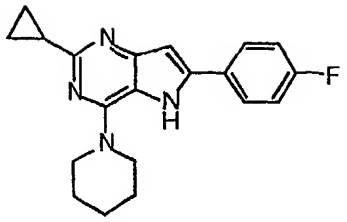
(a) 2-Cyclopropyl-6-(4-fluorophenyl)pyrrolo[3,2-*d*] pyrimidin-4-ol.

This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-(4-fluorophenyl)pyrrole-2-carboxylate (Example 73(a)) (1.05 g, 4.2 mmol), dry HCl gas in cyclopropylcyanide (40 g) and then 6% aqueous sodium hydroxide (30 mL) and ethanol (70 mL) to give 1.41 g of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6; 400 MHz): d 0.77-0.83 (m, 4), 1.32 (m, 1), 1.75 (m, 1), 6.54 (s, 1), 7.09-7.14 (m, 2), 7.77-7.81 (m, 2), 11.85 (br s, 1), 12.04 (br s, 1). MS *m/z*: 270.5 (M+1).



(b) 4-Chloro-2-cyclopropyl-6-(4-fluorophenyl)pyrrolo [3,2-*d*]pyrimidine.

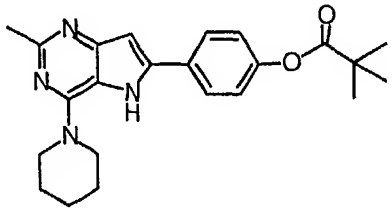
This compound was prepared according to the method described in Example 68 (b) by employing 2-cyclopropyl-6-(4-fluorophenyl)pyrrolo[3,2-*d*]pyrimidin-4-ol (Example 209(a)) (1.14 g, 4.23 mmol), $POCl_3$ (8 mL, 85 mmol) and benzyltriethylammonium chloride (0.48 g, 2.1 mmol) to give 0.97 g (80%) of the title compound as an orange solid. ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.06-1.11 (m, 2), 1.18-1.22 (m, 2), 2.31-2.35 (m, 1), 6.83 (s, 1), 7.17-7.22 (m, 2), 7.74-7.77 (m, 2), 9.15 (br s, 1).



(c) 2-Cyclopropyl-6-(4-fluorophenyl)-4-piperidyl pyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate.

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-cyclopropyl-6-(4-fluorophenyl)pyrrolo[3,2-*d*]pyrimidine (Example 209(b)) (437 mg, 1.5 mmol), piperidine (Aldrich Chemical Company) (0.75 mL, 7.6 mmol), and K_2CO_3 (1.05 g, 7.6 mmol) in H_2O (10 mL) to give 399 mg (78%) of the free base as a beige solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.2 mL, 1.2 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH/H_2O to give 0.14 g of the title compound as off-white crystals. Mp: >280 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.34-1.41 (m, 4), 1.88 (m, 6), 2.37-2.41 (m, 1), 4.18 (m, 4), 7.09 (s, 1), 7.62 (t, 2, J = 8.8), 8.21-8.25 (m, 2), 12.14 (br s, 1). MS *m/z*: 337 (M+1). Anal. Calcd for $C_{20}H_{21}FN_4 \cdot HCl \cdot 0.25H_2O$: C, 63.80; H, 6.00; N, 14.88; Cl, 9.42. Found: C, 63.82; H, 5.97; N, 14.91; Cl, 9.70.

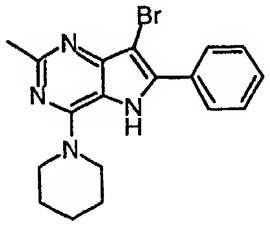
Example 210



4-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl) phenyl 2,2-dimethylpropanoate.

To the mixture of 2-methyl-4-piperidyl-6-(4-hydroxyphenyl)pyrrolo[3,2-*d*]pyrimidine (example 72) (385 mg, 1.25 mmol) and pyridine (5 mL) in a 25-mL, round-bottomed flask was added trimethylacetic anhydride (Aldrich Chemical Company) (0.3 mL, 1.5 mmol). The reaction mixture was heated at reflux for 24 h under a stream of N_2. After cooling to room temperature, the solvent was evaporated *in vacuo* and the residue was partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layers were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica gel with 100:2.5 $CHCl_3$/MeOH as eluant to give 417 mg (85%) of a brown solid. It was recrystallized in EtOH to give 87 mg of the title compound as white solids. Mp: 272-274 °C. MS *m/z*: 393.0 (M+1). ^{1}H NMR ($CDCl_3$; 400 MHz): d 1.38 (s, 9), 1.76 (m, 6), 2.60 (s, 3), 3.79 (m, 4), 6.72 (s, 1), 7.17 (d, 2, J = 8.6), 7.65 (d, 2, J = 8.6), 8.06 (br s, 1). Anal. Calcd for $C_{23}H_{28}N_4O_2$: C, 70.38; H, 7.19; N, 14.27. Found: C, 70.52; H, 7.20; N, 14.32.

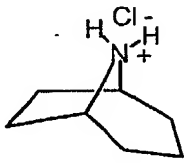
Example 211



7-Bromo-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*] pyrimidine Hydrochloride.

To an oven-dried, 50-mL, round-bottomed flask was added 2-methyl-6-phenyl-4-(piperidinyl)pyrrolo[3,2-*d*]pyrimidine (Example 35)) (500 mg, 1.71 mmol) which was dissolved in glacial AcOH (15 mL). To this

solution was added Br_2 (Aldrich Chemical Company) (90.0 mL, 1.8 mmol) dropwise over 2 min. The resulting dark mixture was diluted with H_2O (10 mL) and the mixture was warmed to 45 °C and stirred for 2 h. The reaction was allowed to cool to room temperature and the crude material was extracted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (3 x 50 mL). The organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to give an oily residue. The residue was purified by silica gel chromatography with 50% EtOAc/hexanes as eluant to give 500 mg (79.4% yield) of a yellow solid. Mp: 239-240 °C. ^1H NMR (DMSO-d_6; 400 MHz): d 1.74 (s, 6), 2.63 (s, 3), 3.83 (s, 4), 7.44 (t, 1, J = 2.4), 7.5 (t, 2, J = 7.0), 7.80 (d, 2, J = 7.1). MS *m/z*: 373.0 (M+1); 369.0, 371.0 (M-1).

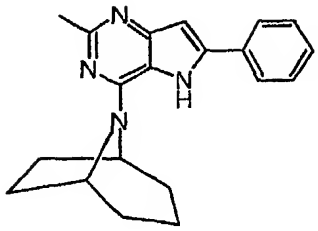


Example 212

(a) 8-Azabicyclo[3.2.1]octane Hydrochloride.

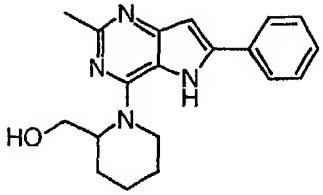
To an oven-dried, 100-mL, round-bottomed flask was added tropane (2.5 g, 19.96 mmol) followed by toluene (20 mL), and a-chloro-ethyl chloroformate (3.2 mL, 30 mmol). The flask was purged with N_2 and the mixture was heated at 120 °C for 16 h. The reaction was allowed to cool to room temperature and the solvent was evaporated *in vacuo*. The resulting residue was dissolved in MeOH (20 mL) and heated to reflux at 85 °C for 3 h. The solvent was evaporated *in vacuo* and the product dried under vacuum to give 2.90 g (98% yield) of a light brown solid. MS *m/z*: 112.0 (M+1). ^1H NMR

(DMSO-d_6; 400 MHz): d 1.64 (m, 4), 1.95 (m, 6), 3.92 (s, 2), 9.24 (br d, 2, J = 7.3).



(b) 4-(8-azabicyclo[3.2.1]oct-8-yl)-2-methyl-6-phenyl pyrrolo[3,2-*d*]pyrimidine Hydrochloride.

To an oven-dried, 50-mL, round-bottomed flask was added $NaOCH_3$ (250 mg, 1.03 mmol) and 8-azabicyclo[3.2.1]octane hydrochloride (Example 212(a)) (152 mg, 1.03 mmol) and the resulting mixture was stirred at room temperature for 30 min. To this mixture was added 4-chloro-2-methyl-6-phenylpyrrolo [3,2-*d*]pyrimidine (Example 1(e)) (125 mg, 0.513 mmol) and the mixture was heated to 180 °C for 4 h. The reaction was allowed to cool to room temperature and the crude material was purified by silica gel chromatography with 50% EtOAc/hexanes as eluant to give 95 mg (60% yield) of light brown solid. The free base (88.0 mg, 0.277 mmol) was dissolved in hot EtOAc (10 mL) and anhydrous ethereal HCl (0.28 mL, of a 1.0 M soln, 0.28 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high vacuum to give 65 mg (66% yield) of the title compound as a light brown solid. Mp: >300 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.32 (m, 4), 2.63 (s, 3), 3.37 (s, 6), 5.26 (s, 2), 6.94 (s, 1), 7.61 (m, 3), 8.0 (d, J = 7.0, 2), 11.84 (s, 1), 14.2 (s, 1). MS *m/z*: 387.5 (M+1); 385.5 (M-1).

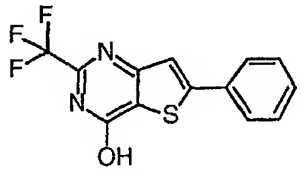


Example 213

(1-[2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)-2-piperidyl)methan-1-ol Hydrochloride.

To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*] pyrimidine (Example 1(e)) (250 mg, 1.03 mmol) and 2-hydroxymethyl piperidine (Aldrich Chemical Company) (237 mg, 2.06 mmol). The flask was purged with N_2 and the mixture was heated to 180 °C for 16 h. The reaction was allowed to cool to room temperature and the crude material was purified by silica gel chromatography with EtOAc as eluant to give 125 mg (38% yield) of an off white solid. ^{1}H NMR ($CDCl_3$; 400 MHz); d 1.74 (m, 6), 2.59 (s, 3), 3.1 (m, 1), 3.8 (m, 1), 4.35 (t, 1, *J* = 10.9), 4.55 (m, 2), 6.72 (s, 1), 7.44 (m, 3), 7.65 (d, *J* = 7.3), 9.9 (br, 1). MS *m/z*: 323.5 (M+1); 321.5 (M-1).

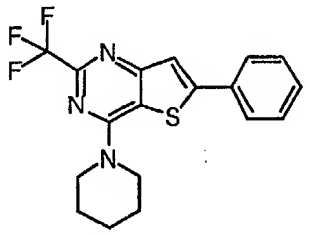
Example 214



(a) 6-Phenyl-2-(trifluoromethyl)thiophene[3,2-*d*] pyrimidin-4-ol.

To an oven-dried, 100-mL, round-bottomed flask was added methyl 3-amino-5-phenylthiophene-2-carboxylate (Maybridge Chemical Company) (1.00 g, 4.29 mmol) along with trifluoroacetamidine (560 mg, 5 mmol) and the mixture was heated to 190 °C for 16 h. A solid

formed in the reaction and as the mixture was allowed to cool to room temperature. Ethanol (50 mL) was added to the reaction mixture and the solid filtered off and dried under vacuum to give 420 mg (33% yield) of a white solid. Mp: 245-246 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): d 7.38 (m, 1), 7.48 (m, 2), 7.58 (dd, 1, *J* = 1, 6.8), 7.67 (s, 1), 7.72 (dd, 2, *J* = 1.2, 6.4). MS *m/z*: 297.0 (M+1); 295.0 (M-1).

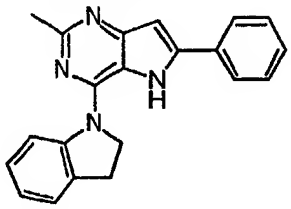


(b) 6-Phenyl-4-piperidyl-2-(trifluoromethyl)thiophene [3,2-*d*]pyrimidine Hydrochloride.

To an oven-dried, 50-mL, round-bottomed flask was added methanesulfonylimidazole (prepared by the method described by J. Michalski and co-workers *Phosphorus and Sulfur* 1986, *26*, 321.) (67 mg, 0.372 mmol) and THF (10 mL), which was cooled to 0 °C with stirring under N_2. To this solution was added methyl triflate (Aldrich Chemical Company) (42 mL, 0.375 mmol) dropwise. The resulting mixture was stirred at 0 °C for 30 min before a solution of 6-phenyl-2-(trifluoromethyl)thiophene [3,2-*d*]pyrimidin-4-ol (Example 214(a)) (100 mg, 0.338 mmol) and 1-methylimidazole (22 mL, 0.281 mmol) dissolved in THF (5 mL) was added. The resulting solution was allowed to warm to room temperature over the course of 2 h, and piperidine (0.25 mL. 2.5 mmol) was added dropwise. The mixture was stirred for 30 min and then dissolved in $CHCl_3$ (50 mL). The organic layer was washed with brine (3 x 50 mL), dried over $MgSO_4$, filtered, and evaporated to give a residue. The residue was purified by silica gel chromatography with 20% EtOAc/hexanes as eluant to give 80 mg (67% yield)

as a light yellow solid. The free base (48 mg, 0.132 mmol) was dissolved in hot CH_2Cl_2 (5 mL) and anhydrous ethereal HCl (0.132 mL, of an 1.0 M soln, 0.132 mmol) was added. The solid was filtered off and dried under vacuum to give 50 mg (95% yield) of a yellow solid. Mp: 168-169 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.7 (br, s, 6), 4.0 (s, 4), 7.52 (m, 3H), 7.91 (d, 2, J = 7.16), 8.03 (s, 1). MS m/z: 323.5 (M+1); 321.5 (M-1).

Example 215

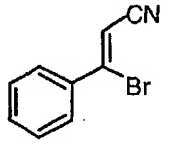


4-Indolinyl-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate.

To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*] pyrimidine (Example 1(e)) (350 mg, 1.44 mmol) and indoline (Aldrich Chemical Company) (350 mg, 2.94 mmol). The flask was purged with N_2 and the mixture was heated to 180 °C for 1 h. The reaction was allowed to cool to room temperature and the crude material was purified by silica gel chromatography with 33% EtOAc/hexanes to give 250 mg (53% yield) of an off white solid. The free base (221 mg, 0.677 mmol) was dissolved in hot EtOAc (15 mL)and MeOH (2 mL) and anhydrous ethereal HCl (0.677 mL, of a 1.0 M soln, 0.677 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high vacuum to give 239 mg (97% yield) of the title compound as a light yellow solid. Mp: > 300 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 2.7 (s, 3), 4.87 (t,

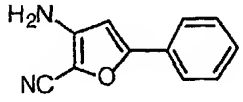
2, J = 8.2), 7.0 (s, 1), 7.17 (t, 1, J = 7.5), 7.32 (t, 1, J = 7.6), 7.58 (m, 3), 8.0 (d, 2, J = 6.9), 8.53 (d, 1, J = 3.3), 11.7 (br, 1), 14.55 (br, 1). *MS m/z*: 327.0 (M+1); 325 (M-1) . Anal. Calcd for $C_{21}H_{18}N_4 \cdot 1.0HCl \cdot 1.25H_2O$: C, 65.45; H, 5.62; N, 14.54. Found: C, 65.62; H, 5.62; N, 14.49.

Example 216



(a) (2*Z*)-3-Bromo-3-phenylprop-2-enenitrile.

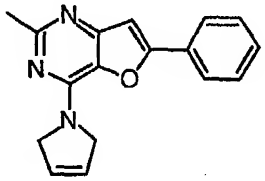
To an oven-dried, 250-mL, round-bottomed flask was added benzolyacetonitrile (Avocado Chemical Company) (5.00g, 34.4 mmol) and PBr_3 (100 mL), and the resulting mixture was heated at 170 °C with stirring under N_2. After 48 h, the mixture was allowed to cool to room temperature and was carefully poured into ice (500 g) and $CHCl_3$ (250 mL) was added. The mixture was stirred for 1 h. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (125 mL). The organic layers were combined and washed with saturated $NaHCO_3$ (3 x 200 mL) and brine (250 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give 8.00 g (98% yield) of a black oil. ^1H NMR ($CDCl_3$; 400 MHz): d 6.35 (s,1), 7.6 (d, J = 6.3,2), 7.4 (m,3).



(b) 3-Amino-5-phenylfuran-2-carbonitrile.

To an oven-dried, 150-mL, round-bottomed flask was added glycolonitrile (Aldrich Chemical Company) (4.6 g, 55 wt. % in H_2O, 24.04 mmol), followed by THF (100 mL), and $MgSO_4$ (10 g). The mixture was stirred for 1 h before a soln of (2Z)-3-bromo-3-phenylprop-2-enenitrile

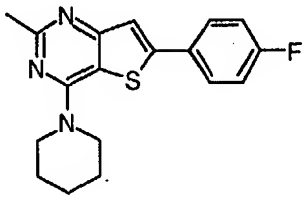
(Example 216(a)) (2.5 g, 12.04 mmol)was added. The mixture was stirred rapidly at room temperature as NaH (1.0 g, 60% in mineral oil, 25 mmol) was carefully added in portions over 1 h. The mixture was poured into ice (100 g) and stirred for 10 min. The reaction was extracted with a mixture of 3:1 of $CHCl_3$:*i*-PrOH (3 x 75 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and evaporated to give 2.0g (90.5% yield) of an oil. ^1H NMR ($CDCl_3$; 400 MHz): d 4.01 (br, 2), 6.35 (s, 1), 7.4 (m, 3), 7.63 (d, 2, *J* = 7.1).



(c) 2-Methyl-6-phenyl-4-(3-pyrrolinyl)furano[3,2-*d*] pyrimidine Hydrochloride Hydrate.

To an oven-dried, 150-mL, round-bottomed flask was added *N,N*-dimethylacetamide (1.02 mL, 11 mmol) followed by $POCl_3$ (50 mL). the mixture was stirred at room temperature for 1 h. To this mixture was added 3-amino-5-phenylfuran-2-carbonitrile (Example 216 (b)) (677 mg, 3.68 mmol). The resulting mixture was heated at 160 °C for 36 h. The solvent was evaporated *in vacuo* and toluene (50 mL) was added. The solvent was again evaporated *in vacuo* and to the crude residue was added 3-pyrroline (Aldrich Chemical Company) (2.00 g, 28.9 mmol). The reaction was then heated to 120 °C for 1 h and then allowed to cool to room temperature. The crude material was dissolved in $CHCl_3$ (100 mL) and washed with saturated $NaHCO_3$ (3 x 100 mL), brine (100 mL), and dried over $MgSO_4$. The organic layer was filtered, and evaporated *in vacuo* to give a residue which was purified by silica gel chromatography with 50% EtOAc/hexanes as eluant. The product was isolated

in 550 g (54% yield) as a light yellow solid. The free base (510 mg, 1.84 mmol) was dissolved in hot EtOAc (20 mL) and anhydrous ethereal HCl (1.85 mL, 1.0 M soln, 1.85 mmol) was added dropwise. A precipitate formed immediately and the mixture was allowed to cool to room temperature. The solid was filtered and dried under vacuum to give 565 mg (95% yield) of the title compound. Mp: 279-280 °C. ^{1}H NMR (DMSO-d_6; 500 MHz): d 2.65 (s, 3), 4.58 (s, 2), 5.01 (s, 2), 6.13 (d, 2, J = 20), 7.59 (m, 3), 7.65 (s, 1), 8.13 (d, 2, J = 5.9). MS m/z: 278.0 (M+1). Anal. Calcd for $C_{17}H_{15}N_3O \cdot 1.10HCl \cdot 1.1H_2O$: C, 60.54; H, 5.47; N, 12.46; Cl, 11.56. Found: C, 60.58; H, 5.41; N, 12.44; Cl, 11.38.

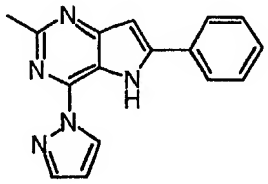


Example 217

6-(4-Fluorophenyl)-2-methyl-4-piperidylthiopheno[3,2-*d*] pyrimidine Hydrochloride Hydrate.

To an oven-dried, 150-mL, round-bottomed flask was added *N,N*-dimethylacetamide (1.07 mL, 11.5 mmol) followed by $POCl_3$ (50 mL). The mixture was stirred at room temperature for 1 h. To this mixture was added 3-amino-2-cyano-5-(4-fluorophenyl)thiophene (Maybridge Chemical Company) (2.5 g, 11.45 mmol) and the resulting mixture was heated at reflux for 36 h. The reaction was allowed to cool to room temperature and the solvent was evaporated *in vacuo*. The residue was suspended in toluene (50 mL) and again the solvent was evaporated at reduced pressure. Approximately 500 mg of residue was removed and added to an oven-dried, 50-mL, round-bottomed flask, followed by piperidine (10 mL). The flask was purged with N_2, and heated to 160 °C for 2 h.

The flask was allowed to cool to room temperature and the crude material was purified by silica gel chromatography with 33% EtOAc/hexanes to give 250 mg of a light yellow solid. The free base (223 mg, 0.681 mmol) was dissolved in hot EtOAc (10 mL) and anhydrous ethereal HCl (0.68 mL, 1.0 M soln, 0.68 mmol) was added dropwise. A precipitate formed immediately and the reaction was allowed to cool to room temperature and was stirred for an additional 1 h. The light yellow solid was filtered off and dried under vacuum overnight to give 240 mg (97% yield) of a light yellow solid. Mp: 285-287°C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.76 (s,6), 2.63 (s,3), 4.13 (s,4), 7.43 (t,2, J=8.8), 7.8 (s,1), 8.01 (m,2). MS m/z: 328.0 (M+1). Anal. Calcd for $C_{18}H_{18}FN_3S\cdot 1.25HCl\cdot 0.5H_2O$: C, 65.48; H, 5.35; N, 10.98; Cl, 11.64. Found: C, 56.48; H, 5.40; N, 10.94; Cl, 11.64.

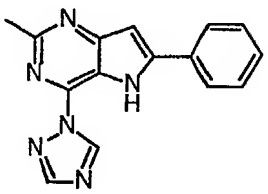


Example 218

2-Methyl-6-phenyl-4-pyrazolypyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate.

To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*] pyrimidine (Example 1(e)) (350 mg, 1.44 mmol) followed by pyrazole (Aldrich Chemical Company) (196 mg, 2.88 mmol) and solid Na_2CO_3 (610 mg, 5.76 mmol). The flask was purged with N_2 and heated to 190-200 °C for 4 h. The reaction was allowed to cool to room temperature and the residue was dissolved in MeOH (25 mL). The remaining salts were filtered off and the organic layer evaporated under reduced pressure. The residue was purified by silica gel chromatography with EtOAc as

eluant to give 245 mg (62% yield) of an off white solid. The free base (238 mg, 0.865 mmol) was dissolved in hot EtOAc (15 mL) and anhydrous ethereal HCl (0.87 mL, 1.0 M soln, 0.87 mmol) was added dropwise. A precipitate formed and the reaction was allowed to cool to room temperature and stirred for 1 h. The solid was filtered off and dried under vacuum at 60 °C overnight to give 250 mg (93% yield) of an off white solid. Mp: 253-254°C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 2.8 (s, 3), 6.83 (s, 1), 7.23 (s, 1), 7.58 (m, 3), 8.12 (d, 2, J = 6.4), 8.22 (s, 1), 8.88 (d, 1, J = 2.5), 12.0 (br s, 1). MS m/z: 276.0 (M+1). Anal. Calcd for $C_{16}H_{13}N_5 \cdot 1.11HCl \cdot 0.9H_2O$: C, 57.86; H, 4.83; N, 21.09; Cl, 11.88. Found: C, 58.01; H, 4.88; N, 20.79; Cl, 11.88.

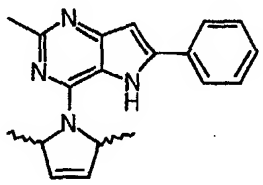


Example 219

2-Methyl-6-phenyl-4-[1,2,4-triazolyl]pyrrolo[3,2-*d*] pyrimidine Hydrochloride.

To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*] pyrimidine (Example 1(e)) (350 mg, 1.44 mmol) followed by 1,2,4-triazole (Aldrich Chemical Company) (200 mg, 2.88 mmol) and solid Na_2CO_3 (610 mg, 5.76 mmol). The flask was purged with N_2 and heated to 190-200 °C for 4 h. The reaction was allowed to cool to room temperature and the residue was dissolved in MeOH (25 mL). The remaining salts were filter off and the organic layer evaporated under reduced pressure. The residue was purified by silica gel chromatography with 50% EtOAc/hexanes as eluant to give 180 mg (45% yield) of an off white solid. The free base (168 mg, 0.608

mmol) was dissolved in hot EtOAc (15 mL) and anhydrous ethereal HCl (0.61 mL, 1.0 M soln, 0.61 mmol) was added dropwise. A precipitate formed and the reaction was allowed to cool to room temperature and stirred for 1 h. The solid was filtered off and dried under vacuum at 60 °C overnight to give 182 mg (96% yield) of an off white solid. Mp: 264-265 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 2.77 (s, 3), 7.22 (s, 1), 7.57 (m, 3), 8.10 (d, 2, J = 5.5), 8.6 (d, 1, J = 3.4), 9.64 (d, 1, J = 4.2), 11.87 (br m, 1). MS m/z: 277.0 (M+1); 275 (M-1).



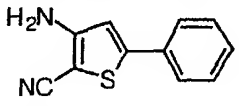
Example 220

4-(2,5-Dimethyl(3-pyrrolinyl)-2-methyl-6-phenylpyrrolo [3,2-*d*]pyrimidine Hydrochloride Hydrate.

To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*] pyrimidine (Example 1(e)) (600 mg, 2.46 mmol) and a *cis* and *trans* mixture of 2,5-dimethyl-3-pyrroline (Aldrich Chemical Company) (717 mg, 7.38 mmol). The flask was purged with N_2 and the mixture was heated to 180 °C for 1 h. The reaction was allowed to cool to room temperature and the crude material triturated with MeOH to give 550 mg (73% yield) of an off white solid. The free base (500 mg, 1.64 mmol) was dissolved in hot EtOAc (15 mL)and MeOH (2 mL) and anhydrous ethereal HCl (1.64 mL, of a 1.0 M soln, 1.64 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high vacuum to give 550 mg (98% yield) of the title compound as a light yellow solid. Mp: 242-243 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): d

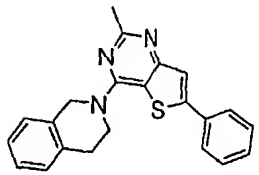
1.42 (d, 6, J = 6.3), 2.54 (s, 3), 5.14 (br, 1), 5.65 (br, 1), 6.00 (s, 2), 6.84 (s, 1), 7.5 (m, 3), 7.85 (d, 2, J = 7.0). MS m/z: 358 (M+1). Anal. Calcd for $C_{19}H_{20}N_4$.1.0 HCl.0.90 H_2O: C, 63.91; H, 6.44; N, 15.69; Cl, 9.93. Found: C, 64.01; H, 6.20; N, 15.5; Cl, 9.78.

Example 221



(a) 3-Amino-5-phenylthiophene-2-carbonitrile.

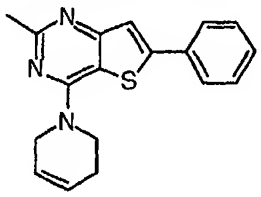
To an oven-dried, 50-mL, round-bottomed flask was added acetylmercaptoacetonitrile (Maybridge Chemical Company) (2.00 g, 17.37 mmol), followed by anhydrous EtOH (50 mL) and the dropwise addition of $NaOCH_3$ (5.64 g, 21 wt. %, 17.37 mmol). The resulting mixture was stirred for 1 h at room temperature, and then cooled to -78 °C with a dry ice/acetone bath. To this solution was added an ethanolic solution of vinyl bromide example 33 a (3.8 g, 18.26 mmol) in anhydrous EtOH (10 mL) at -78 °C. After stirring for 1 h at this temperature, the reaction was allowed to warm to room temperature and was stirred for an additional 2 h. The solvent was evaporated under reduced pressure to leave a residue. The residue was dissolved in $CHCl_3$ (100 mL) and washed with 2.0 N NaOH (3 x 75 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to give a brown solid in 3.4 g (98% yield). ^1H NMR (DMSO-d_6; 400 MHz): d 4.48 (br, 2), 6.75 (s, 1), 7.39 (m, 3), 7.53 (dd, 2, J = 2, 6). MS m/z: 201 (M+1).



(b) 2-Methyl-6-phenyl-4-[2-1,2,3,4-tetrahydro isoquinolyl)thiopheno[3,2-*d*]pyrimidine Hydrochloride Hydrate.

To an oven-dried, 150-mL, round-bottomed flask was added *N,N*-dimethylacetamide (Aldrich Chemical Company) (1.07 mL, 11.5 mmol) followed by $POCl_3$ (50 mL). The mixture was stirred at room temperature for 1 h. To this mixture was added 3-amino-2-cyano-5-phenyl thiophene (Example 221(a)) (2.5 g, 11.45 mmol) and the resulting mixture was heated at reflux for 36 h. The reaction was allowed to cool to room temperature and the solvent was evaporated *in vacuo*. The residue was suspended in toluene (50 mL) and again the solvent was evaporated at reduced pressure. Approximately 750 mg of residue was removed and added to an oven-dried, 50-mL, round-bottomed flask, followed by 1,2,3,4-tetrahyrdoisoquinoline (4.0 mL, 31.9 mmol). The flask was purged with N_2, and heated to 160 °C for 2 h. The flask was allowed to cool to room temperature and the crude material was purified by silica gel chromatography with 25% EtOAc/hexanes to give 250 mg of a light yellow solid. The free base (500 mg, 1.4 mmol) was dissolved in hot EtOAc (20 mL) and anhydrous ethereal HCl (1.4 mL, 1.0 M soln, 1.4 mmol) was added dropwise. A precipitate formed immediately and the reaction was allowed to cool to room temperature and was stirred for an additional 1 h. The light yellow solid was filtered off and dried under vacuum overnight to give 540 mg (98% yield) of a light orange solid. Mp: 263-265 °C. ^1H NMR (DMSO-d_6; 400 MHz): d 2.55 (s, 3), 3.00 (s, 2), 4.19 (t, 2, J = 5.7), 5.15 (s, 2), 7.17 (m, 3), 7.28 (d, 1, J = 4.0), 7.45 (m, 3), 7.71 (s, 1), 7.80 (m, 2). MS *m/z*: 375.0 (M+1). Anal. Calcd for $C_{22}H_{19}N_3S \cdot 1.0HCl \cdot 0.88H_2O$: C, 64.38; H, 5.35; N, 10.24; Cl, 8.77. Found: C, 64.38; H, 5.10; N, 10.14; Cl, 8.76.

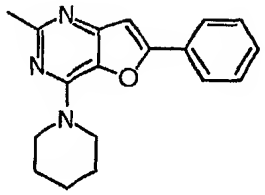
Example 222



2-Methyl-6-phenyl-4-(1,2,5,6-tetrahydropyridyl) thiopheno[3,2-*d*]pyrimidine Hydrochloride Hydrate.

To an oven-dried, 150-mL, round-bottomed flask was added *N,N*-dimethylacetamide (Aldrich Chemical Company) (1.07 mL, 11.5 mmol) followed by $POCl_3$ (50 mL). The mixture was stirred at room temperature for 1 h. To this mixture was added 3-amino-2-cyano-5-phenyl thiophene (Example 221(a)) (2.5 g, 11.45 mmol) and the resulting mixture was heated at reflux for 36 h. The reaction was allowed to cool to room temperature and the solvent was evaporated *in vacuo*. The residue was suspended in toluene (50 mL) and again the solvent was evaporated at reduced pressure. Approximately 750 mg of residue was removed and added to an oven-dried, 50-mL, round-bottomed flask, followed by 1,2,3,6-tetrahyrdopyridine (3.0 mL, 32.9 mmol). The flask was purged with N_2, and heated to 160 °C for 2 h. The flask was allowed to cool to room temperature and the crude material was purified by silica gel chromatography with 25% EtOAc/hexanes to give 325 mg of a light yellow solid. The free base (300 mg, 0.976 mmol) was dissolved in hot EtOAc (15 mL) and anhydrous ethereal HCl (1.0 mL, 1.0 M soln, 1.0 mmol) was added dropwise. A precipitate formed immediately and the reaction was allowed to cool to room temperature and was stirred for an additional 1 h. The light yellow solid was filtered off and dried under vacuum overnight to give 320 mg (95.5% yield) of a light yellow solid. Mp: 279-281 °C. ^1H NMR (DMSO-d_6; 400 MHz): d 2.59 (br s, 2), 2.85 (s,

3), 4.42 (t, 2, J = 5.7), 4.87 (s, 2), 6.09 (d, 1, J = 10), 6.23 (d, 1, J = 9.9), 7.78 (m, 3), 8.04 (s, 1), 8.15 (m, 2). MS *m/z*: 308.0 (M+1). Anal. Calcd for $C_{18}H_{17}N_3S \cdot 1.0HCl \cdot 0.65H_2O$: C, 60.73; H, 5.47; N, 11.81; Cl, 10.05. Found:C, 60.73; H, 5.32; N, 11.61; Cl, 9.95.



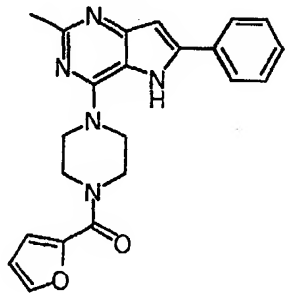
Example 223

2-Methyl-6-phenyl-4-piperidylfurano[3,2-*d*]pyrimidine Hydrochloride Hydrate.

To an oven-dried, 150-mL, round-bottomed flask was added *N,N*-dimethylacetamide (1.02 mL, 11 mmol) followed by $POCl_3$ (50 mL). The mixture was stirred at room temperature for 1 h. To this mixture was added 3-amino-5-phenylfuran-2-carbonitrile (Example 216(b)) (677 mg, 3.68 mmol). The resulting mixture was heated at 160 °C for 36 h. The solvent was evaporated *in vacuo* and toluene (50 mL) was added. The solvent was again evaporated *in vacuo* and to the crude residue was added piperidine (Aldrich Chemical Company) (3.00 mL, 30.3 mmol). The reaction was then heated to 160 °C for 1 h and then allowed to cool to room temperature. The crude material was dissolved in $CHCl_3$ (100 mL) and washed with saturated $NaHCO_3$ (3 x 100 mL), brine (100 mL), and dried over $MgSO_4$. The organic layer was filtered, and evaporated *in vacuo* to give a residue which was purified by silica gel chromatography with 50% EtOAc/hexanes as eluant. The product was isolated in 200 mg (19% yield) as a light yellow solid. The free base (181 mg, 0.617 mmol) was dissolved in hot EtOAc (20 mL) and anhydrous ethereal HCl (0.617 mL, 1.0 M soln, 0.617 mmol) was added dropwise. A precipitate

formed immediately and the mixture was allowed to cool to room temperature. The solid was filtered and dried under vacuum to give 198 mg (97% yield) of the title compound. Mp: > 290 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 1.75 (br s, 6), 2.58 (s, 3), 4.16 (s, 4), 7.61 (m, 4), 8.08 (d, 2, J = 6.8). MS m/z: 294.0 (M+1). Anal. Calcd for $C_{18}H_{19}N_3O$•1.08 HCl•1.82 H_2O. C, 59.11; H, 6.54; N, 11.49; Cl, 10.51. Found:C, 59.11; H, 6.19; N, 11.42; Cl, 10.62.

Example 224

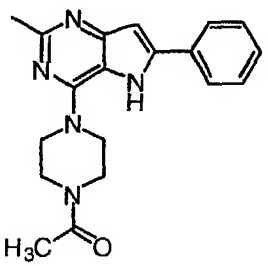


1-(2-Furanylcarbonyl)-4-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)piperazine Hydrochloride Monohydrate.

To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d] pyrimidine (Example 1(e)) (500 mg, 2.05 mmol) and the 1-(2-furoyl)piperazine (Avocado Chemical Company) (810 mg, 4.10 mmol). The flask was purged with N_2 and the mixture was heated to 180 °C for 30 min. The reaction was allowed to cool to room temperature and the crude material was purified by flash chromatography on silica gel with 50% EtOAc/$CHCl_3$ as eluant to give 500 mg (63% yield) of an off white solid. The free base (200 mg, 0.52 mmol) was dissolved in hot EtOAc (10 mL) and anhydrous ethereal HCl (0.52 mL, of a 1.0 M soln, 0.52 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high

vacuum to give 205 mg (96% yield) of the title compound as a light yellow solid. Mp: 192-193 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 2.54 (s, 3), 3.89 (br s, 4), 4.17 (t, 4, J = 4.3), 6.62 (q, 1, J = 1.7), 6.9 (s, 1), 7.05 (d, 1, J = 3.4), 7.4 (m, 3), 7.85 (s, 1), 7.93 (d, 2, J = 6.92). MS m/z: 388 (M+1). Anal. Calcd for $C_{22}H_{21}N_5O_2 \cdot HCl \cdot H_2O$: C, 59.79; H, 5.47; N, 15.85; O, 10.86; Cl, 8.02. Found: C, 59.99; H, 5.33; N, 15.79; Cl, 8.06.

Example 225

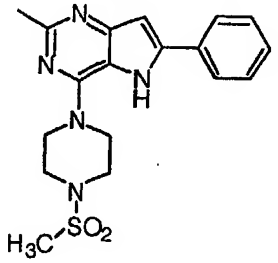


1-Acetyl-4-(2-methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)piperazine Hydrochloride.

To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*] pyrimidine (Example 1(e)) (500 mg, 2.05 mmol) and 1-acetyl-piperazine (Aldrich Chemical Company) (525 mg, 4.10 mmol). The flask was purged with N_2 and the mixture was heated to 180 °C for 30 min. The reaction was allowed to cool to room temperature and the crude material was purified by flash chromatography on silica gel with 10% MeOH/EtOAc as eluant to give 600 mg (87% yield) of an off white solid. The free base (400 mg, 1.2 mmol) was dissolved in hot EtOAc (10 mL) and anhydrous ethereal HCl (1.2 mL, of a 1.0 M soln, 1.2 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high vacuum to give 205 mg (96% yield) of the title compound

as a light yellow solid. Mp: 282-283 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): d 2.09 (s, 3), 2.61 (s, 3), 3.7 (s, 4), 4.14 (dt, J = 5.3, 14), 6.95 (s, 1), 7.54 (m, 3), 8.00 (d, 2, J = 6.88). MS m/z: 366 (M+1); 364 (M-1). Anal. Calcd for $C_{19}H_{21}N_5O\cdot HCl$.: C, 60.76; H, 5.95; N, 18.65; O, 4.45; Cl, 10.19. Found: C, 60.76; H, 5.90; N, 18.64; Cl, 10.15.

Example 226

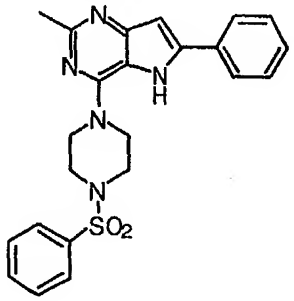


1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)-4-(methylsulfonyl)piperazine Hydrochloride Monohydrate.

To an oven-dried, 50-mL, round-bottomed flask was added 2-methyl-6-phenyl-4-piperazinylpyrrolo[3,2-d] pyrimidine (Example 26) (400 mg, 1.36 mmol) was suspended in anhydrous THF (20 mL) and Et_3N (0.4 mL, 2.8 mmol) was added. The mixture was cooled to 0 °C and methanesulfonyl chloride (Aldrich Chemical Company) (0.12 mL, 1.5 mmol) was added dropwise and allowed to warm to room temperature over 30 min. EtOAc (50 mL) was added to the mixture which was extracted with saturated $NaHCO_3$ (3 x 50 mL). The organic layer was washed with saturated NaCl (75 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 450 mg (89% yield) as a light yellow solid. The free base (440 mg, 1.2 mmol) was dissolved in hot EtOAc (20 mL) and anhydrous ethereal HCl (1.18 mL, of a 1.0 M soln, 1.18 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high

vacuum to give 460 mg (95.6% yield) of the title compound as a light yellow solid. Mp: 280-282 °C. ^1H NMR (DMSO-d_6; 400 MHz); d 2.54 (s, 3), 2.88 (s, 3), 3.29 (s, 4), 4.13 (t, 4, J = 4.62), 6.9 (s, 1), 7.51 (m, 3), 7.94 (d, 2, J = 6.85). MS m/z: 372 (M+1); 370 (M-1). Anal. Calcd for $C_{18}H_{21}N_5O_2S \cdot HCl \cdot H_2O$.: C, 50.46; H, 5.70; N, 16.35; Cl, 8.41. Found: C, 50.71; H, 5.60; N, 16.22; Cl, 8.45.

Example 227

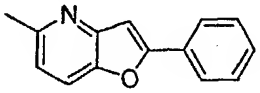


1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl(phenyl sulfonyl)piperazine Hydrochloride Monohydrate.

To an oven-dried, 50-mL, round-bottomed flask was added 2-methyl-6-phenyl-4-piperazinylpyrrolo[3,2-*d*] pyrimidine (Example 26) (400 mg, 1.36 mmol) was suspended in anhydrous THF (20 mL) and Et_3N (0.4 mL, 2.8 mmol) was added. The mixture was cooled to 0 °C and benzenesulfonyl chloride (Aldrich Chemical Company) (0.19 mL, 1.5 mmol) was added dropwise and allowed to warm to room temperature over 30 min. EtOAc (50 mL) was added to the mixture which was extracted with saturated $NaHCO_3$ (3 x 50 mL). The organic layer was washed with saturated NaCl (75 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 450 mg (89% yield) as a light yellow solid. The free base (500 mg, 1.15 mmol) was dissolved in hot EtOAc (20 mL) and anhydrous ethereal HCl (1.15 mL, of a 1.0 M soln, 1.15 mmol) was added dropwise. The mixture was stirred for

2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high vacuum to give 510 mg (94.1% yield) of the title compound as a light yellow solid. Mp: 242-243 °C. ^1H NMR (DMSO-d_6; 400 MHz); d 2.4 (s, 3), 2.98 (t, 4, J = 4.6), 4.00 (t, 4, J = 4.7), 6.75 (s, 1), 7.37 (m, 3), 7.49 (t, 2, J = 7.8), 7.57 (t, 1, J = 7.5), 7.62 (d, 2, J = 7.2), 7.81 (d, 2, J = 6.7). MS *m/z*: 434 (M+1); 432 (M-1). Anal. Calcd for $C_{23}H_{24}N_5O_2S \cdot HCl \cdot H_2O$: C, 56.63; H, 5.37; N, 14.36; Cl, 7.27. Found: C, 56.63; H, 5.37; N, 14.27; Cl, 7.41.

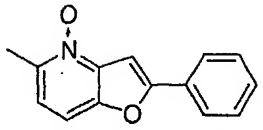
Example 228



(a) 5-Methyl-2-phenylfurano[3,2-b]pyridine.

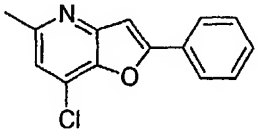
A mixture of 6-iodo-2-picolin-5-ol (Aldrich Chemical Company) (1.00 g, 4.29 mmol), phenylacetylene (Aldrich Chemical Company) (0.66 mL, 6.01 mmol), $Cl_2Pd(PPh_3)_2$ (15.1 mg, 0.21 mmol) and CuI (41.0 mg, 0.21 mmol) in Et_3N (20 mL) was heated under reflux (100 °C) for 16 h. Heating was discontinued and after cooling the mixture was diluted with CH_2Cl_2 (100 mL) and NH_4Cl (50 mL). The mixture was transferred to a separatory funnel. The organic solution was collected, washed with saturated NH_4Cl (50 mL) and saturated NaCl (50 mL). The organic solution was collected, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 821 mg (91%) of the title compound as a white colored solid. ^1H NMR ($CDCl_3$; 400 MHz): δ 2.63 (s, 3), 7.07 (d, 1, J = 8.4), 7.15 (s, 1), 7.40 (dt, 1, J = 2.1, 7.4), 7.47 (t, 2, J = 7.8), 7.67 (d,

1, *J* = 8.6), 7.90 (dd, 2, *J* = 1.5, 7.2). MS *m/z* : 210 (M+1).



(b) 5-Methyl-2-phenylfurano[3,2-b]pyridine *N*-oxide.

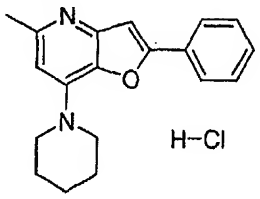
A mixture of 5-methyl-2-phenylfurano[3,2-b] pyridine (Example 228(a)) (507 mg, 2.43 mmol) and *m*-chloroperbenzoic acid (0.84 g, purity 60%, 2.91 mmol) in $CHCl_3$ (20 mL) was stirred at 25 °C for 18 h. The mixture was filtered slowly through a fritted funnel with a basic alumina (20 g) pad. The pad was washed with $CHCl_3$ (50 mL) and the organic solutions were combined and concentrated under reduced pressure to afford 517 mg (95%) of the title compound as a white colored solid. ^1H NMR ($CDCl_3$; 400 MHz): δ 2.64 (s, 3), 7.15 (d, 1, *J* = 8.4), 7.40 (d, 1, *J* = 8.4), 7.43 - 7.51 (m, 4), 7.89 (dd, 2, *J* = 1.4, 7.0). MS *m/z* : 226 (M+1).



(c) 7-Chloro-5-methyl-2-phenylfurano[3,2-b]pyridine.

To a mixture of 5-methyl-2-phenylfurano[3,2-b] pyridine *N*-oxide (Example 228(b)) (302 mg, 1.33 mmol) in $CHCl_3$ (4 mL) was added $POCl_3$ (1.3 mL, 13.3 mmol). The mixture was heated to 60 °C where it was stirred for 16 h. After cooling the reaction mixture was poured onto crushed ice (50 mL). The pH of the mixture was adjusted to pH 8 with the slow addition of saturated $NaHCO_3$ (15 mL). $CHCl_3$ (30 mL) was added and the mixture was transferred to a separatory funnel. The organic solution was collected and the aqueous solution washed with $CHCl_3$ (2 x 30 mL). The organic solutions were combined, dried over $MgSO_4$, filtered and

concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 25:75 EtOAc:hexanes as elutant to give 220 mg (68%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 2.63 (s, 3), 7.10 (s, 1), 7.15 (s, 1), 7.43 (t, 1, *J* = 7.3), 7.49 (t, 2, *J* = 7.8), 7.93 (d, 2, *J* = 7.9). MS *m/z* : 244 (M+1).

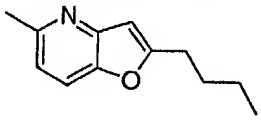


(d) 5-Methyl-2-phenyl-7-piperidylfurano[3,2-b]pyridine hydrochloride.

To a mixture of 7-chloro-5-methyl-2-phenylfurano [3,2-b]pyridine (Example 228(c)) (365 mg, 1.50 mmol) and piperidine (5 mL, 50.5 mmol) was added DMF (2 mL). Mixture stirred at 120 °C under N_2 for 26 h. After cooling, the reaction mixture was concentrated. The residue was diluted with H_2O (70 mL) and Et_2O (50 mL). The mixture was transferred to a separatory funnel and the organic solution was collected. The aqueous solution was washed with Et_2O (2 x 40 mL). The organic solutions were combined, washed with H_2O (50 mL), saturated NaCl (70 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 300 mg (68%) of 5-methyl-2-phenyl-7-piperidylfurano[3,2-b]pyridine as a cream colored solid. This material (298 mg, 1.02 mmol) was dissolved in EtOAc (20 mL) and heated to boiling. To the hot solution was added 1M etheral HCl (1.00 mL, 1.00 mmol). The solution was left to cool to 25 °C. The resulting solid was collected by filtration, washed with EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum at 25 °C to give 290 mg (59%) of the title

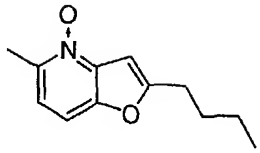
compound as a white colored powder. Mp: >280 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.67 (br s, 6), 2.49 (s, 3), 3.94 (br s, 4), 6.93 (s, 1), 7.46 - 7.54 (m, 4), 7.98 (dd, 2, J = 1.5, 7.6), 14.14 (s, 1). MS m/z : 293 (M+1 for free base). Anal. Calcd for $C_{19}H_{20}N_2O \cdot HCl \cdot 0.25H_2O$: C, 68.46; H, 6.50; N, 8.41; Cl, 10.64. Found C, 68.60; H, 6.44; N, 8.43; Cl, 10.56.

Example 229



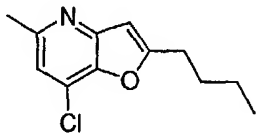
(a) 2-Butyl-5-methylfurano[3,2-b]pyridine.

A mixture of 6-iodo-2-picolin-5-ol (Aldrich Chemical Company) (1.49 g, 6.33 mmol), 1-hexyne (Aldrich Chemical Company) (1.02 mL, 8.86 mmol), $Cl_2Pd(PPh_3)_2$ (220 mg, 0.32 mmol) and CuI (60.0 mg, 0.32 mmol) in Et_3N (25 mL) was heated under reflux (90 °C) for 18 h. Heating was discontinued and after cooling the mixture was diluted with CH_2Cl_2 (100 mL) and NH_4Cl (50 mL). The mixture was transferred to a separatory funnel. The organic solution was collected, washed with saturated NH_4Cl (50 mL) and saturated NaCl (50 mL). The organic solution was collected, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 1.08 g (92%) of the title compound as a yellow colored oil. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 0.94 (t, 3, J = 7.4), 1.43 (hextet, 2, J = 7.5), 1.74 (quintet, 2, J = 7.6), 2.62 (s, 3), 2.79 (t, 2, J = 7.6), 6.52 (s, 1), 6.99 (d, 1, J = 8.4), 7.53 (d, 1, J = 8.4). MS m/z : 190 (M+1).



(b) 2-Butyl-5-methylfurano[3,2-b]pyridine *N*-oxide.

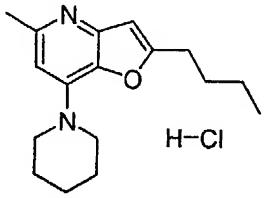
A mixture of 2-butyl-5-methylfurano[3,2-b]pyridine (Example 229(a)) (1.06 g, 5.61 mmol) and *m*-chloroperbenzoic acid (1.94 g, purity 60%, 6.73 mmol) in $CHCl_3$ (50 mL) was stirred at 25 °C for 18 h. The mixture was filtered slowly through a fritted funnel with a basic alumina (30 g) pad. The pad was washed with $CHCl_3$ (50 mL) and the organic solutions were combined and concentrated under reduced pressure to afford 1.14 g (99%) of the title compound as a yellow colored oil. ^1H NMR ($CDCl_3$; 400 MHz): δ 0.95 (t, 3, *J* = 7.3), 1.41 (hextet, 2, *J* = 7.4), 1.74 (quintet, 2, *J* = 7.5), 2.60 (s, 3), 2.81 (t, 2, *J* = 7.5), 6.86 (s, 1), 7.07 (d, 1, *J* = 8.4), 7.26 (d, 1, *J* = 8.4). MS *m/z* : 207 (M+1).



(c) 2-Butyl-7-chloro-5-methylfurano[3,2-b]pyridine.

To a mixture of 2-butyl-5-methylfurano[3,2-b] pyridine *N*-oxide (Example 229(b)) (1.13 g, 5.51 mmol) in $CHCl_3$ (3 mL) was added $POCl_3$ (5.1 mL, 55.1 mmol). The mixture was heated to 80 °C where it was stirred for 16 h. After cooling the reaction mixture was poured onto crushed ice (100 mL). The pH of the mixture was adjusted to pH 8 with the slow addition of saturated $NaHCO_3$ (150 mL). $CHCl_3$ (150 mL) was added and the mixture was transferred to a separatory funnel. The organic solution was collected and the aqueous solution washed with $CHCl_3$ (2 x 70 mL). The organic solutions were combined, dried over $MgSO_4$, filtered and

concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 10:90 EtOAc:hexanes as elutant to give 671 mg (54%) of the title compound as a white colored solid. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 0.96 (t, 3, J = 7.4), 1.43 (hextet, 2, J = 7.4), 1.76 (quintet, 2, J = 7.5), 2.60 (s, 3), 2.83 (t, 2, J = 7.7), 6.54 (s, 1), 7.02 (s, 1). MS m/z : 224 (M+1).

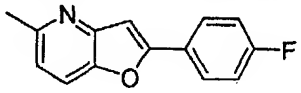


(d) 2-Butyl-5-methyl-7-piperidylfurano[3,2-b]pyridine hydrochloride.

To a mixture of 2-butyl-7-chloro-5-methylfurano [3,2-b]pyridine (Example 229(c)) (329 mg, 1.45 mmol) and piperidine (3 mL, 30.4 mmol) was added a mixture of K_2CO_3 (0.85 g, 5.8 mmol) in H_2O (1 mL). Mixture stirred at 100 °C under N_2 for 16 h. After cooling, the reaction mixture was concentrated. The residue was diluted with H_2O (70 mL) and Et_2O (50 mL). The mixture was transferred to a separatory funnel and the organic solution was collected. The aqueous solution was washed with Et_2O (2 x 40 mL). The organic solutions were combined, washed with H_2O (50 mL), saturated NaCl (70 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 310 mg (77%) of 2-butyl-5-methyl-7-piperidylfurano[3,2-b]pyridine as a cream colored solid. This material (310 mg, 1.12 mmol) was dissolved in EtOAc (10 mL) and heated to boiling. To the hot solution was added 1M etheral HCl (1.20 mL, 1.20 mmol). The solution was left to cool to 25 °C. The resulting solid was collected by filtration, washed

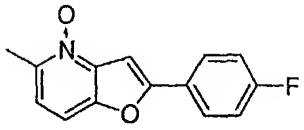
with EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum at 25 °C to give 311 mg (69%) of the title compound as a white colored powder. Mp: 172 - 173 °C. ^1H NMR ($CDCl_3$; 400 MHz): δ 0.95 (t, 3, *J* = 7.4), 1.42 (hextet, 2, *J* = 7.3), 1.69 (quintet, 2, *J* = 7.7), 1.79 (br s, 6), 2.71 (s, 3), 2.79 (t, 2, *J* = 7.5), 3.85 (br , 4), 6.29 (s, 1), 7.01 (s, 1), 15.56 (s, 1). MS *m/z* : 2793 (M+1 for free base). Anal. Calcd for $C_{17}H_{24}N_2O \bullet HCl \bullet 0.5H_2O$: C, 64.24; H, 8.25; N, 8.82; Cl, 11.15. Found C, 64.42; H, 8.23; N, 8.75; Cl, 11.26.

Example 230 and Example 231



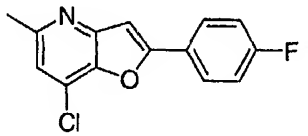
(a) 2-(4-Fluorophenyl)-5-methylfurano[3,2-b]pyridine.

A mixture of 6-iodo-2-picolin-5-ol (Aldrich Chemical Company) (1.38 g, 5.86 mmol), 1-ethynyl-4-fluorobenzene (Aldrich Chemical Company) (0.99 g, 8.21 mmol), $Cl_2Pd(PPh_3)_2$ (205 mg, 0.29 mmol) and CuI (56 mg, 0.29 mmol) in Et_3N (25 mL) was heated under reflux (90 °C) for 16 h. Heating was discontinued and after cooling the mixture was diluted with CH_2Cl_2 (100 mL) and NH_4Cl (50 mL). The mixture was transferred to a separatory funnel. The organic solution was collected, washed with saturated NH_4Cl (50 mL) and saturated NaCl (50 mL). The organic solution was collected, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 1.17 g (88%) of the title compound as a white colored solid. ^1H NMR ($CDCl_3$; 400 MHz): δ 2.66 (s, 3), 7.08 (s, 1), 7.17 (t, 2, *J* = 6.7), 7.66 (d, 1, *J* = 8.3), 7.84 - 7.89 (m, 2). MS *m/z* : 228 (M+1).



(b) 2-(4-Fluorophenyl)-5-methylfurano[3,2-b]pyridine *N*-oxide.

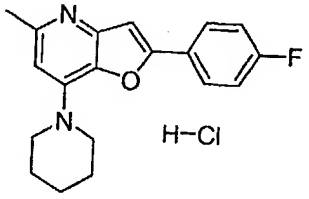
A mixture of 2-(4-fluorophenyl)-5-methylfurano [3,2-b]pyridine (Example 230(a)) (1.15 g, 5.07 mmol) and *m*-chloroperbenzoic acid (1.75 g, purity 60%, 6.08 mmol) in $CHCl_3$ (40 mL) was stirred at 25 °C for 18 h. The mixture was filtered slowly through a fritted funnel with a basic alumina (40 g) pad. The pad was washed with $CHCl_3$ (2 x 50 mL) and the organic solutions were combined and concentrated under reduced pressure to afford 1.23 mg (95%) of the title compound as a white solid. ^1H NMR ($CDCl_3$; 400 MHz): δ 2.63 (s, 3), 7.13 - 7.21 (m, 3), 7.39 (d, 1, *J* = 8.4), 7.41 (s, 1), 7.85 - 7.89 (m, 2). MS *m/z* : 244 (M+1).



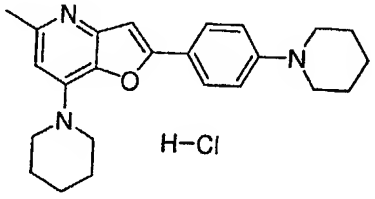
(c) 7-Chloro-2-(4-fluorophenyl)-5-methylfurano[3,2-b] pyridine.

To a mixture of 2-(4-fluorophenyl)-5-methylfurano [3,2-b]pyridine *N*-oxide (Example 230(b)) (1.22 g, 5.02 mmol) in $CHCl_3$ (2 mL) was added $POCl_3$ (5.0 mL, 50.2 mmol). The mixture was heated to 100 °C where it was stirred for 8 h. After cooling the reaction mixture was poured onto crushed ice (50 mL). The pH of the mixture was adjusted to pH 8 with the slow addition of saturated $NaHCO_3$ (100 mL). $CHCl_3$ (100 mL) was added and the mixture was transferred to a separatory funnel. The organic solution was collected and the aqueous solution washed with $CHCl_3$ (2 x 70 mL). The organic solutions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was

purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 775 mg (59%) of the title compound as a white colored solid. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 2.63 (s, 3), 7.09 (s, 1), 7.11 (s, 1), 7.18 (t, 2, J = 8.6), 7.89 - 7.93 (m, 2). MS m/z : 262 (M+1).



Example 230



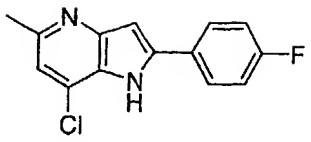
Example 231

(d) 2-(4-Fluorophenyl)-5-methyl-7-piperidylfurano[3,2-b] pyridine hydrochloride (Example 230) and 5-Methyl-7-piperidyl-2-(4-piperidylphenyl)furano[3,2-b]pyridine hydrochloride (Example 231).

To a mixture of 7-chloro-5-methyl-2-phenylfurano [3,2-b]pyridine (Example 230(c)) (370 mg, 1.43 mmol) and piperidine (5 mL, 50.5 mmol) was added DMF (2 mL). Mixture stirred at 120 °C under N_2 for 24 h. After cooling, the reaction mixture was concentrated. The residue was diluted with H_2O (70 mL) and Et_2O (50 mL). The mixture was transferred to a separatory funnel and the organic solution was collected. The aqueous solution was washed with Et_2O (2 x 40 mL). The organic solutions were combined, washed with H_2O (50 mL), saturated NaCl (70 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 132 mg (30%) of 2-(4-fluorophenyl)-5-methyl-7-piperidylfurano[3,2-b]pyridine as a cream colored solid and 35 mg (7%) of 5-methyl-7-piperidyl-2-(4-piperidylphenyl)furano[3,2-b]pyridine as a tan colored solid.

Example 230: 2-(4-Fluorophenyl)-5-methyl-7-piperidylfurano[3,2-b]pyridine (132 mg, 0.42 mmol) was dissolved in EtOAc (5 mL) and heated to boiling. To the hot solution was added 1M etheral HCl (0.50 mL, 0.5 mmol). The solution was left to cool to 25 °C. The resulting solid was collected by filtration, washed with EtOAc (2 x 2 mL), Et_2O (3 x 5 mL) and dried under vacuum at 25 °C to give 130 mg (27%) of the title compound as a cream colored powder. Mp: >280 °C. ^1H NMR (DMSO-d_6; 400 MHz): δ 1.68 (br s, 6), 2.48 (s, 3), 3.94 (br s, 4), 6.95 (s, 1), 7.39 (t, 2, J = 8.6), 7.50 (s, 1), 8.07 (m, 2), 13.85 (s, 1). MS *m/z* : 311 (M+1 for free base). Anal. Calcd for $C_{19}H_{19}FN_2O \cdot HCl \cdot 0.25H_2O$: C, 64.95; H, 5.88; N, 7.98; Cl, 10.09. Found C, 65.18; H, 5.86; N, 7.93; Cl, 10.13.

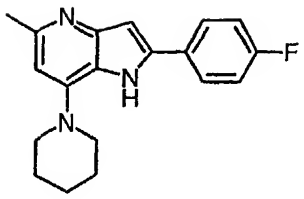
Example 231: 5-Methyl-7-piperidyl-2-(4-piperidyl phenyl)furano[3,2-b]pyridine (31.0 mg, 0.08 mmol) was dissolved in EtOAc (5 mL) and heated to boiling. To the hot solution was added 1M etheral HCl (0.20 mL, 0.20 mmol). The solution was left to cool to 25 °C. The resulting solid was collected by filtration, washed with EtOAc (2 x 2 mL), Et_2O (3 x 5 mL) and dried under vacuum at 25 °C to give 30 mg (6%) of the title compound as a brown colored solid. Mp: decomposition >170 °C. ^1H NMR (DMSO-d_6; 400 MHz): δ 1.54 (br s, 6), 1.64 (br s, 6), 2.43 (s, 3), 3.29 (br s, 4), 3.89 (br s, 4), 6.85 (s, 1), 7.10 (m, 1), 7.22 (s, 1), 7.80 (m, 2), 13.75 (s, 1). MS *m/z* : 376 (M+1 for free base). Anal. Calcd for $C_{24}H_{29}N_3O \cdot 2HCl \cdot 2.5H_2O$: C, 58.41; H, 7.35; N, 8.52; Cl, 14.37. Found C, 58.30; H, 7.28; N, 8.38; Cl, 14.18.



Example 232

(a) 7-Chloro-5-methyl-2-(4-fluorophenyl)pyrrolo-[3,2-b] pyridine.

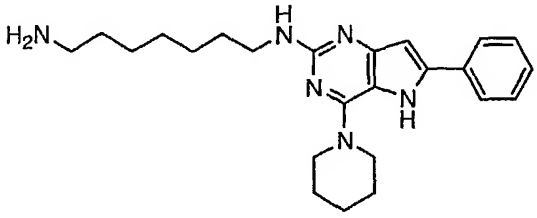
To a solution of 3-amino-2,4-dichloro-6-methyl pyridine (5.3 g, 28.2 mmol) in NEt_3 (190 mL), was added $(PPh_3)_2PdCl_2$ (1.4 g, 2.1 mmol), and CuI (400 mg, 2.2 mmol). The mixture was cooled to 0 °C and a solution of 4-fluorophenylacetylene (4.5 g, 37.5 mmol) in 10 mL of DMF was added slowly via syringe. The mixture was allowed to warm to room temperature then heated at 80 °C for 96 h. The mixture was allowed to cool to room temperature and filtered through a short pad of celite. The celite was rinsed with NEt_3 and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 1:4 EtOAc:hexanes to afford 2.91 g (40%) of starting material followed by 2.97 g (55%, 91% based on recovered starting material) of 3-Amino-4-chloro-6-methyl-2-(2-phenylethynyl)pyridine as a dark brown solid. MS *m/z*: 243 (M+1). The crude intermediate (2.90 g, 11.1 mmol) was dissolved in anhydrous DMF (250 mL), CuI (310 mg, 16.3 mmol) was added and the mixture was heated at 95 °C for 19 h. The reaction mixture was cooled to room temperature and the crude product was collected by filtration. Chromatography on silica with 8:1 $CHCl_3$:MeOH gave 1.6 g (54%, 30% over two steps) of 7-chloro-5-methyl-2-(4-fluorophenyl)pyrrolo-[3,2-b]pyridine. ^1H NMR (DMSO-d_6; 500 MHz): d 2.50 (s, 3), 6.99 (s, 1), 7.11 (s,1), 7.32 (t, 2, J = 8.8), 8.05 (m, 2), 11.78 (s, 1). MS *m/z*: 262 (M+H).



(b) 5-Methyl-2-(4-fluorophenyl)-7-piperidylpyrrolo[3,2-b]pyridine.

A mixture of 7-chloro-5-methyl-2-(4-fluorophenyl) pyrrolo[3,2-b]pyridine (1.5 g, 5.9 mmol) in 3:1 *o*-xylene/piperidine (20 mL) was heated at 140 °C in a Teflon-capped pressure tube for 5 d. The mixture was allowed to cool to room temperature, diluted with 5 mL of a 5:1 mixture of $CHCl_3$:MeOH and run through a short column of silica eluting with 10:1 $CHCl_3$:MeOH. The filtrate was concentrated *in vacuo*, the crude product was dissolved in 20 mL of $CHCl_3$ and 1M HCl in ether (8.0 mL, 8.0 mmol) was added slowly via syringe. The mixture was dried by rotary evaporation and triturated with a 1:5 mixture of EtOH:EtOAc. Filtration and drying under high vacuum for 24 h gave 1.45 g (70%) of the title compound as a yellow solid. ^1H NMR (DMSO-d_6; 500 MHz): d 1.72 (b s, 6), 2.55 (s, 3), 3.76 (s, 4), 6.80 (s, 1), 6.89 (s,1), 7.40 (t, 2, J = 8.8), 8.02 (m, 2), 11.82 (s, 1), 13.79 (s, 1). Anal. Calcd for $C_{19}H_{20}F_1N_3 \bullet HCl \bullet 0.5H_20$: C, 64.31; H, 6.25; N, 11.84. Found: C, 63.95; H, 6.15; N, 12.21.

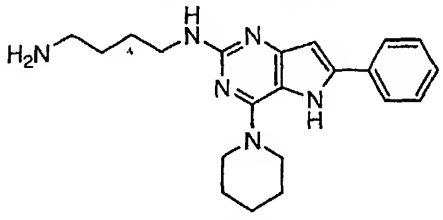
Example 233



(7-Aminoheptyl)-(6-phenyl-4-piperidylpyrrolo[3,2-d] pyrimidin-2-yl)amine Hydrochloride Hydrate.

To a sealed 5-mL vial was added 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (Example 203(c)) (55 mg, 0.176 mmol), 1,7-diaminoheptane (Aldrich Chemical Company) (92 mg, 0.703 mmol) and pyridine (1.5 mL). The solution was heated at 150 °C for 3 h. The reaction mixture was allowed to cool to room temperature and pyridine was removed *in vacuo*. The resulting residue was washed with sat. $NaHCO_3$, and extracted with $CHCl_3$ three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography on silica gel with $MeOH/CH_2Cl_2/NH_4OH$(4:95:1) as eluant to afford 30mg (42%) of a light-brown solid. The free base (30 mg, 0.074 mmol) was dissolved in CH_2Cl_2 (2 mL) and anhydrous ethereal HCl (0.11mL of a 2 M soln, 0.22mmol) was added dropwise. The precipitate was collected by filtration, washed with EtOAc/ether (1:1) (3 x 1 mL) and dried over vacuum to give 25 mg (66 %) of the title compound as a light brown solid. ^1H NMR (DMSO-d_6;400 MHz): d 1.30-1.20 (m, 16), 2.90-2.95 (m, 2), 3.55-3.60 (m, 2), 4.11 (s, 4), 6.83 (s, 1), 7.60-8.30 (m, 9). MS *m/z* : 407 (M+1). Anal. Calcd for $C_{24}H_{34}N_6 \cdot 3HCl \cdot H_2O$: C, 54.00; H, 7.36; N, 15.74. Found: C, 54.20; H, 7.02; N, 14.46.

Example 234



(4-Aminobutyl)-(6-phenyl-4-piperidylpyrrolo[3,2-d] pyrimidin-2-yl)amine Hydrochloride Hydrate.

To a sealed 3-mL vial was added 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (Example 203(c))

(56 mg, 0.18 mmol), 1,4-diaminobutane(Aldrich Chemical Company) (158 mg, 1.80 mmol) and pyridine (0.5 mL). The solution was heated at 150 °C for 6 h. The reaction mixture was allowed to cool to room temperature and pyridine was removed *in vacuo*. The resulting residue was washed with sat. $NaHCO_3$, and extracted with $CHCl_3$ three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography on silica gel with $MeOH/CH_2Cl_2/NH_4OH$ (4:95:1) as eluant to afford 25 mg (38 %) of a light-brown solid. The free base (30 mg, 0.074 mmol) was dissolved in CH_2Cl_2 (2 mL) and anhydrous ethereal HCl (0.10 mL of a 2 M soln, 0.20 mmol) was added dropwise. The precipitate was collected by filtration, washed with EtOAc/ether (1:1) (3 x 0.5 mL) and dried over vacuum to give 25 mg (77 %) of the title compound as a light brown solid. ^1H NMR (MeOH-d_6; 400 MHz): d 1.90-2.10 (m,10), 3.20-3.20 (m,2), 3.70-3.80 (m,2), 4.20-4.30 (m,4), 6.84 (s,1), 7.70-8.20 (m,5). MS *m/z*: 365 (M+1). Anal. Calcd for $C_{21}H_{28}N_6 \cdot 3HCl \cdot H_2O$: C, 51.28; H, 6.76; N, 17.08. Found: C, 52.00; H, 6.81; N, 15.01.

Biological Studies

Feeding Studies in Mice

Protocol For Icv Administration Of Compounds In Ad-Lib Fed OB/OB Female Mice.

Eight week old (approx. 50g) OB/OB female mice were obtained from Jackson Laboratories (Bar Harbor, ME) and given one week to acclimate to the animal facility before the experiment. Animals were housed 10 per cage and were provided with food and water ad-lib. Immediately prior to injection, animals were removed from group housing and lightly anesthetized using 4%

isofluorane vapor. Freehand intracerebroventricular ("icv") injection of compounds was done in a 100% DMSO vehicle in a volume of 5 µl. Immediately following the injection, animals were placed in individual cages and were provided with a pre-weighed portion of regular chow pellets. Total amount of food consumed was measured at 1, 2, 4 and 24 hours post-injection.

The results show a statistically significant decrease in food intake in obese animals:

I.C.V. treatment	4 hr food intake (g ± S.E.M.)
vehicle	0.61 ± 0.10
Example 35	0.29 ± 0.11*

*significantly different from vehicle, $p < 0.05$

Protocol for mice studies

Protocol For IP Administration Of Compounds In Male BALB-C Mice.

Male BALB-C mice (20-25 g)were obtained from Charles Rivers (Wilmington, MA) and were given at least a one week acclimation period to Amgen's animal care facilities. Animals were housed 10/cage and were provided ad libitum food and water. For testing, mice were fasted for 18-20 hr (overnight) prior to the start of the experiment. On the day of the experiment, mice were removed from group housing and placed into individual cages (without food). Test compounds or vehicle was then administered via the intraperitoneal (i.p.) route of administration. Test compounds were suspended in a 2% tween solution; the 2% tween solution was used as the vehicle treatment (control group). Group sizes for each treatment were 6-8 animals. After 30 min, premeasured food was placed into the cages. Two hours later, the food was weighed again. The difference between 2 hr weight and the premeasured weight was taken as 2 hr food intake. The following

compounds showed at least a 10% inhibition of feeding in the mouse model at 30 mg/kg (ip): Examples 9, 30, 32, 33, 35, 61, 63, 64, 65, 66e, 68c, 69c, 71e, 72, 73a, 76c, 77, 80d, 81d, 85, 92d, 93, 95c, 96, 97, 98, 101, 103, 107, 108, 111, 114, 116, 118, 119, 121, 122, 123, 124, 125, 130, 131, 194, 195d, 196c, 197, 198, 199, 215, 217, 218 and 232b.

Feeding Studies in Rats

Protocol For Icv Administration Of Compounds In Food-Deprived Long-Evans Male Rats

Adult male Long-Evans rats (approx. 275g) were obtained from Charles River Laboratories (Wilmington, MA) and given one week to acclimate to the animal facility. Animals were housed individually and given ad-lib access to food and water. After acclimation, animals were anesthetized (75 mg/kg Sodium Nembutal) and implanted with 23g cannulas (Plastics One, Roanoke, VA) into the right lateral cerebral ventricle. All animals were given at least 1 week post-operative recover before any experiment.

Animals were food deprived for 16 hours prior to injections. Intracerebroventricular injection of compounds was done in awake, unrestrained animals in a DMSO vehicle in a volume of 20 µl. Immediately following the injection, the animals were returned to their home cage and were provided with a pre-weighed portion of regular rat chow pellets. Total food consumed was measured at 2 and 4 hours post-injection.

The results show a statistically significant decrease in food intake in food deprived animals:

I.C.V. treatment	4 hr food intake (g ± S.E.M.)
vehicle	8.69 ± 0.53
Example 1f	5.13 ± 1.40*

*significantly different from vehicle, $p < 0.05$

Protocol For Icv Administration Of NPY Antagonists Against pNPY Induced Feeding In Satiated Long-Evans Male Rats

Adult male Long-Evans rats (approx. 275g) were obtained from Charles River Laboratories (Wilmington, MA) and given one week to acclimate to the animal facility. Animals were housed individually and given ad-lib access to food and water. After acclimation, animals were anesthetized (75 mg/kg Sodium Nembutal) and implanted with 23g cannulas (Plastics One, Roanoke, VA) into the right lateral cerebral ventricle. All animals were given at least 1 week post-operative recover before any experiment.

Approximately 16 hours prior to injection, animals were provided with access to 30 grams of a sucrose/condensed milk/rat chow mash along with their regular chow. Ninety minutes prior to injections, regular chow was removed from the cages and animals were provided with a fresh portion of the high sucrose mash. Intracerebroventricular injection of antagonist or vehicle was done in awake, unrestrained animals in a DMSO vehicle in a volume of 20 µl. Approximately 15 minutes after the administration of the antagonist or vehicle, animals were given a second 5 µl injection of either water or pNPY. After the second injection, the portion of high sucrose mash was weighed and total food consumed was measured at 2 and 4 hours post-injection.

The results show the ability of the compounds of the invention to significantly inhibit NPY induced feeding behavior in animals:

I.C.V. treatment	4 hr food intake (g ± S.E.M.)
vehicle	5.29 ± 0.97
Example 2	3.35 ± 0.62*

*significantly different from vehicle, $p < 0.05$

Protocol For IP Administration Of Compounds In Fasted Long-Evans Male Rats

Male Long Evans rats (85-100 g)were obtained from Harlan (Indianapolis, IN) and were given at least a one week acclimation period to Ambients animal care facilities. Animals were individually housed and were provided ad libitum food and water. For testing, rats were fasted for 18-20 hr (overnight) prior to the start of the experiment. On the test day, test compounds or vehicle was administered via the intraperitoneal (i.p.) route of administration. Test compounds were suspended in a 2% tween solution; the 2% tween solution was used as the vehicle treatment (control group). Group sizes for each treatment were 6-8 animals. After 30 min, premeasured food was placed into the cages. Two hours later, the food was weighed again. The difference between 2 hr weight and the premeasured weight was taken as 2 hr food intake. The following compounds showed at least a 10% inhibition of feeding in the mouse model at 30 mg/kg (ip): Examples 32, 33, 35, 61, 63, 65, 66e, 68c, 69c, 70e, 71e, 72, 76c, 80d, 85, 90, 95c, 96, 97, 101, 102, 104, 108, 111, 116, 118, 119, 121, 122, 123, 124, 126, 127, 134, 137, 141, 142, 143, 148, 150, 160, 168, 194, 195, 196c, 197d, 198, 200d, 202, 203, 209c, 216c, 217 and 232b.

Protocol For MCP-1 Inhibition Assay

Compounds of this invention may be shown to inhibit monocyte chemoattractant protein 1 (MCP-1) binding using the methods described in WO 98/06703 (incorporated herein by reference in its entirety). Membranes for use the MCP-1 inhibition assay can be prepared as follows. Human monocytic leukemia cell line, THP-1, cells are centrifuged, washed twice in ice-cold PBS (phosphate-buffered saline), resuspended

in ice-cold lysis buffer (5mM HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)), pH 7.5, 2 mM EDTA, 5 ug/mL leupeptin, 5 ug/mL aprotinin, 5 ug/mL chymostatin and 100 ug/mL phenylmethanesulfonyl fluoride) at a concentration of about 5 x 10^7 cells/mL. The cell suspension is dounced 10-15 times using a B pestle (e.g., small pestle tissue grinder of 0.07 mm clearance) on ice. Nuclei and debris are removed by centrifugation at 500-1000 x g for about 10 minutes at about 4°C. The supernatant is transferred to a fresh tube and centrifuged at 25,000 x g for about 30 minutes at about 4°C. The supernatant is aspirated and the pellet is resuspended in buffer (10mM HEPES, pH 7.5, 300 mM sucrose, 1 ug/mL leupeptin, 1 ug/mL aprotinin, 1 ug/mL chymostatin and 10 ug/mL phenylmethanesulfonyl fluoride) using a minihomogenizer until all clumps are resolved. Membranes are aliquoted and frozen at about -70°C until needed. The total membrane protein can be determined with a standard protein assay, such as Bradford protein assay, BioRad, Richmond, CA.

Assays typically involve mixing about 10-20 ug of total membrane protein, a test compound in DMSO and about 0.2 nM I^{125}-labeled MCP-1 (Amersham, Arlington Heights, IL) in assay buffer (10 mM HEPES, pH 7.2, 1 mM $CaCl_2$, 5 mM $MgCl_2$ and 0.5% BSA) at a final volume of about 100 µl. After about 30-60 minutes at room temperature, the assay is filtered with GF/C filters (Whatman glass fiber filters, Type C) or GF/B unifilter plates (Packard) pre-soaked in 0.3% polyethyleneimine and washed twice with assay buffer containing about 0.5 M NaCl. The filters are dried and counted in a scintillation counter using standard scintillation fluid. Typically, the final concentration of compound in the assay ranges from about 0.05 µM to about 100 µM. Negative controls contain the same concentration of

DMSO present in assays containing compound. Positive controls contain about 250-500 nM cold MCP-1 (Peprotech, Rocky Hill, NJ) in DMSO. IC50 values can be calculated for each compound using a non-linear 3-parameter logistic curve fit. Any observed non-specific binding is subtracted from all data prior to analysis.

Protocols For CRF Antagonist and CRH Binding Protein Inhibition Activity Determination

Compounds of this invention may be shown to antagonize CRF and/or inhibit binding of CRH binding protein using the methods described in WO 98/05661, WO 98/08846 and WO 98/08847 (each of which is incorporated herein by reference in its entirety).

Protocol For Corticotropin Releasing Factor Antagonist Activity Determination

Compounds of this invention may be shown to be antagonists of CRF activity using the methods described in Endocrinology 116:1653-1659 (1985) and Peptides 10:179-188 (1985) (each of which are incorporated herein by reference in their entirety).

Protocol For Corticotropin Releasing Factor Hormone Binding Protein Inhibition Activity Determination

Compounds of this invention may be shown to inhibit CRH binding protein activity using the methods described in Brain Research 745:248-255 (1997) (incorporated herein by reference in its entirety).

Protocols For Protein Kinase Inhibition Activity Determination

Compounds of this invention may be shown to inhibit protein kinases and cell growth using the

methods described in WO 98/07726 (incorporated herein by reference in its entirety).

Protocols For EGF-R-PTK Inhibition Activity Determination

The inhibition of EGF-receptor-specific protein tyrosine kinase (EGF-R-PTK) can be demonstrated using the recombinant intracellular domain of the EGF receptor described in E. McGlynn et al., Europ. J. Biochem. 207:265-275 (1992). Inhibition of EGF-stimulated cellular tyrosine phosphorylation in the EGF-receptor can be shown in the human A431 epithelial carcinoma cell line by means of an ELISA which is described in U. Trinks et al., J. Med. Chem. 37:7, 1015-1027 (1994). U. Trinks et al. also describe a method for testing the inhibition EGF stimulation of quiescent BALB/c3T3 cells to rapidly induce the expression of c-fos mRNA which involves pretreating the cells with test compound

A method (Meyer et al., Int. J. Cancer 43:851 (1989)) for screening compounds for inhibition of the cell growth of EGF-dependent cell lines, such as the epidermoid BALB/c mouse keratinocyte cell line (Weissmann, and Aaronson, Cell 32:599 (1983)), the A431 cell line, a standard source of EGF-dependent epithelial cells (Carpenter and Zendegni, J. Anal. Biochem. 153:279-282 (1985)) and the like, is as follows: BALB/MK cells (about 10,000/microtitre plate well) are transferred to 96-well microtitre plates. A test compound (dissolved in DMSO) is added in a dilution series of concentrations such that the final concentration of DMSO does not exceed 1% (v/v). The plates are incubated for about three days during which the control cultures without test compound are able to undergo at least three cell-division cycles. The growth of the MK cells is measured by means of

Methylene Blue staining (the cells are fixed with glutaraldehyde, washed with water and stained with 0.05% Methylene Blue). After washing, the stain is eluted with 3% HCl and the optical density per well of the microtitre plate is measured, such as with a Titertek Multiscan, at 665 nm. The IC_{50} of the test compound is calculated based on the cell counts.

A method for in vivo screening of compounds for inhibition of the growth of tumour cells, such as the human epidermoid carcinoma A431 (ATCC No. CRL 1555; American Type Culture Collection, Rockville, Maryland, USA; Santon et al., Cancer Research 46:4701-4705 (1986); and Ozawa et al., Int. J. Cancer 40:706-710 (1987)) is as follows. The human epidermoid carcinoma A431 is transplanted into female BALB/c nude mice (Bomholtgard, Denmark). This carcinoma has been reported to exhibit a growth that correlates with the extent of the expression of the EGF-receptor. Tumours having a volume of approximately 1 cm^3 cultured *in vivo* are surgically removed from experimental animals under sterile conditions. These tumours are comminuted and suspended in 10 volumes (w/v) of phosphate-buffered saline. The suspension is injected s.c. (0.2 ml/mouse in phosphate-buffered saline) into the left flank of the animals. Alternatively, 1 x 10^6 cells from an *in vitro* culture in 0.2 ml of phosphate-buffered saline can be injected. Treatment with a test compound is started 5 or 7 days after transplantation, when the tumours have reached a diameter of 4-5 mm. The test compound is administered, at different doses for different animal groups, once a day for 15 successive days. The tumour growth is determined by measuring the diameter of the tumours along three axes that are perpendicular to each other. The tumour volumes can be calculated using the formula p x L x $D^2/6$ (Evans et al., Brit. J. Cancer 45:466-8 (1982)).

Protocols For Determination of Activity Inhibition of Other Protein Kinases

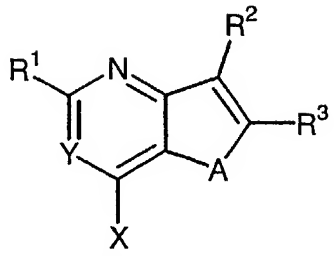
Methods for screening compounds for inhibition of other protein tyrosine kinases that are involved in signal transmission mediated by trophic factors, for example abl kinase (v-abl kinase), kinases from the family of the src kinases (c-src kinase and c-erbB2 kinase (HER-2)), and serine/threonine kinases (protein kinase C), all of which are involved in growth regulation and transformation in mammalian cells, including human cells, are as follows. Inhibition of v-abl tyrosine can be determined using [Val^5]-angiotensin II and [γ-^{32}P]-ATP substrates in the methods of Lydon et al. (Oncogene Research 5:161-173 (1990)) and Geissler et al. (Cancer Research 52:4492-4498 (1992)). The inhibition of c-erbB2 tyrosine kinase (HER-2) can be determined using an analogous method to the above described EGF-R-TPK method (House et al., Europ. J. Biochem. 140:363-367 (1984)). Alternatively, the activity of isolated c-erbB2 kinase can be determined (Akiyama et al., Science 232:1644 (1986)).

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

We Claim:

1. A compound of formula



or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N or $C(R^6)$; A is N-H, $N-R^4$ or CR^4R^7;

R^6 is a hydrogen, -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl or -Z(Q) radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or -Z(Q) radical;

R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or -Z(Q) radical, provided that R^2 is not an optionally substituted phenyl, pyridyl, pyrazinyl, pyrimidyl or pyridazinyl radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_1-C_8)alkyl, $-((C_1-C_8)alkyl)OH$, $(C_1-C_8)alkoxy-(C_1-C_8)alkyl-$,

$-((C_1-C_8)alkyl)N(R^5)_2$, $-((C_1-C_8)alkyl)S(O)_p((C_1-C_8)alkyl)$,
$-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mOH$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)OH$,
$-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$,
$-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mN(R^5)_2$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(O)_pR^5$, $-D'(S(O)_qR^5)$,
-D'(aryloxy), -D'(aryl), -D'(heteroaryl),
$-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^5SO_2R^5)$, $-D'(CON(R^5)_2)$,
$-D'(CO_2R^5)$, $-D'(NR^5CON(R^5)_2)$, $-D'(NR^5(CO)R^5)$, $-D'(NR^5CO_2R^5)$,
$-D'(COR^5)$, -D'(Q), -D(aryloxy), -D(aryl),
-D(heteroaryl), $-D((C_3-C_{10})cycloalkyl)$, $-D(NR^5SO_2R^5)$,
$-D(CON(R^5)_2)$, $-D(CO_2R^5)$, $-D(S(O)_qR^5)$, $-D(NR^5CON(R^5)_2)$,
$-D(NR^5(CO)R^5)$, $-D(NR^5CO_2R^5)$, $-D(COR^5)$ or $-(NR^5)_k$-D—Q
radical;

R^4 is a (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl,
$-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl),
-Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$,
$-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$,
$-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or -Z(Q)
radical;

X is a (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl,
$-(NR^5)_k((C_1-C_8)alkyl)(C_1-C_8)alkoxy$,
$-(NR^5)_k((C_1-C_8)alkyl)aryloxy$, $-(NR^5)((C_1-C_8)alkyl)_kS(O)_pR^5$,
$-(NR^5)_k((C_1-C_8)alkyl)S(O)_pR^5$, $-(NR^5)D(C_1-C_8)alkoxy$,
$-(NR^5)(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$,
$-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^5)(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)aryloxy$,
$-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$,

$-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m$aryloxy, $-Z(S(O)_qR^5)$, $-Z$(aryl), $-Z$(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$ or $-Z(Q)$ radical; or

X and A together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic carbocyclic or heterocyclic ring which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, or (C_1-C_8)alkyl radical;

each R^5 and R^7 are each independently a hydrogen, -OH, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl or (C_3-C_{10})cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 6;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 is optionally substituted with one or more radicals of halo, $-CF_3$, $-OCF_3$, $-Z(COOH)$, $-Z(OH)$,

-Z(NO_2), -Z(SH), -(C_1-C_8)alkyl, -(C_1-C_8)acyloxy, -(C_3-C_{10})cycloalkyl, -S-((C_1-C_8)alkyl)$_k$-aryl, -((C_1-C_8)alkyl)$_k$-SO_2NH-aryl, -S-(C_1-C_8)alkyl, -Z((C_1-C_8)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C_3-C_{10})cycloalkyl), -Z($NR^9SO_2R^9$), -Z($CON(R^9)_2$), -Z(CO_2R^9), -Z($N(R^9)_2$), -Z($NR^9CON(R^9)_2$), -Z($NR^9(CO)R^9$), -Z($NR^9CO_2R^9$), -Z(COR^9), -Z($S(O)_pR^9$) or -Z(Q), wherein each R^9 is independently a hydrogen or (C_1-C_8)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with one or more radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_8)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 0-4; and

provided that:

(a) when A is NH, Y is N, R^1 is H, methyl or phenyl, and R^3 is methyl, ethyl or phenyl, then (1) when R^2 is H, X is not $-NH_2$, $-N(CH_2CH_3)_2$, $-NHCH_2CH_2N(CH_2CH_2)_2$, $-NHCH_2CH_2CH_2CO_2H$, $-NHCH_2CH_2OH$, -NH-phenyl, $-NHCH_2CH_2$-phenyl, -NH-$CH(CH_3)CH_2$-phenyl, -NH-(methoxyphenyl), $-NHCH_2CH_2$-(dimethoxyphenyl), $-NHCH_2CH_2$-imidazolyl, $-NHCH_2CH_2$-(methylthioimidazolyl), $-NHCH_2CH_2$-cyclohexyl, -NH-cyclohexyl, piperidinyl, morpholinyl, $-NHNH_2$, $-NHCH(CH_3)_2$, -NH-butyl, -NH-$CH(CH_3)(CH_2)_4CH_3$, $-NH(CH_2)_2$cyclohexenyl, -NH-$(CH_2)_5CH_3$, $-NHCH_2CH{=}CH_2$, -NH-CH_2-phenyl, 4-methylpiperazine, $-NHSO_2$(4-aminophenyl) or -NH-(4-methylpiperazine); (2) when R^2 is $-CH_2N(CH_2CH_3)_2$, $-CH_2NH$-butyl, $-CH_2NHCH_2CH_2$-cyclohexenyl or $-CH_2NHCH_2CH_2COOH$, X is not $-NH(CH_2)_2$cyclohexenyl; and (3) when R2 is methyl, acetyl or $-COOCH_2CH_3$, X is not $-NH_2$ or $-NH(C(O)CH_3)$;

(b) when R^1 is ethoxy, R^2 is H, R^3 is $-COOCH_2CH_3$, A is NH and Y is N, then X is not $-NH_2$;

(c) when A is N-H or N-R^4, Y is C-H and R^1 is hydrogen, halo, alkyl, cycloalkyl, alkoxy or alkylthio, then (1) when R^3 is methyl and R^2 is acetyl or $-COOCH_3$, X is not NH_2 or trifluoromethylphenyl; (2) when R^3 is methyl or $-COOCH_2CH_3$ and R^2 is H, X is not methyl; and (3) when one of R^2, R^3 or R^4 is optionally substituted -ethyl-NR^5CONHR^5, X is not alkyl or cycloalkyl;

(d) when A is N-R^4 and Y is C-H, then R^3 is not $-CO_2R^5$;

(e) when A is N-C_1-C_6 alkyl, Y is C-H or N, R^1 and R^3 are hydrogen, halo, alkyl, alkoxy or alkylthio, then R^2 is not thienyl optionally substituted with 1-3 halo, hydroxy, alkyl or alkoxy radicals;

(f) when A is CH_2, Y is C-H, R^1 is NH_2, R^3 is methyl and X is methyl, then R^2 is not $C(O)NH_2$;

(g) when A is N-H or N-R^4 and R^3 is aryl or heteroaryl, then R^2 is not aryl or heteroaryl;

(h) when A is N-R^4, Y is N, R^1 is H and R^3 is alkyl, then X is not $-NH_2$; and

(i) when A is N-H or N-R^4 and R^2 is H, then R^3 is not optionally substituted phenyl which is substituted by $-N(R^5)-(C_2-C_6$ alkyl$)-N(R^5)_2$ or $-N(R^5)-(C_2-C_6$ alkyl$)-Q$.

2. The compound of claim 1 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N or $C(R^6)$; A is N-H, N-R^4 or CR^4R^7;

R^6 is a hydrogen, -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)$alkyl$)$, $-N((C_1-C_8)$alkyl$)_2$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl or -Z(Q) radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)$alkoxy$)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl),

$-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$ radical, provided R^1 is not an optionally substituted aryl or heteroaryl radical;

R^2 is a hydrogen, halo, $-OH$, $-NO_2$, $-CF_3$, $-OCF_3$, $(C_1-C_8)alkyl$, $(C_3-C_{10})cycloalkyl$, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$ radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a $(C_3-C_{10})cycloalkyl$, $(C_3-C_8)alkyl$, $-((C_1-C_8)alkyl)OH$, $(C_1-C_8)alkoxy-(C_1-C_8)alkyl-$, $-((C_1-C_8)alkyl)N(R^5)_2$, $-((C_1-C_8)alkyl)S(O)_p((C_1-C_8)alkyl)$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(COR^5)$, $-((C_1-C_8)alkyl)(CO_2R^5)$, $-((C_1-C_8)alkyl)(COR^5)$, $-D'(S(O)_qR^5)$, $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$, $-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^5SO_2R^5)$, $-D'(CON(R^5)_2)$, $-D'(NR^5CON(R^5)_2)$, $-D'(NR^5(CO)R^5)$, $-D'(NR^5CO_2R^5)$, $-D'(Q)$, $-D(aryloxy)$, $-D(aryl)$, $-D(heteroaryl)$, $-D((C_3-C_{10})cycloalkyl)$, $-D(NR^5SO_2R^5)$, $-D(CON(R^5)_2)$,

$-D(S(O)_qR^5)$, $-D(NR^5CON(R^5)_2)$, $-D(NR^5(CO)R^5)$, $-D(NR^5CO_2R^5)$ or $-(NR^5)_k-D-Q$ radical, provided R^3 is not $-SO_2NH_2$;

R^4 is a (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)$alkoxy), $-Z($aryloxy), $-Z($aryl), $-Z($heteroaryl), $-Z((C_3-C_{10})$cycloalkyl), $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$ radical;

X is a $-(NR^5)_k((C_1-C_8)$alkyl$)(C_1-C_8)$alkoxy, $-(NR^5)_k((C_1-C_8)$alkyl$)$aryloxy, $-(NR^5)((C_1-C_8)$alkyl$)_kS(O)_pR^5$, $-(NR^5)_k((C_1-C_8)$alkyl$)S(O)_pR^5$, $-(NR^5)D(C_1-C_8)$alkoxy, $-(NR^5)(CH_2)_m((C_3-C_{10})$cycloalkyl$)_k(CH_2)(C_1-C_8)$alkoxy, $-(NR^5)_k(CH_2)((C_3-C_{10})$cycloalkyl$)_k(CH_2)_m(C_1-C_8)$alkoxy, $-(NR^5)_k(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_m(C_1-C_8)$alkoxy, $-(NR^5)(CH_2)_m((C_3-C_{10})$cycloalkyl$)_k(CH_2)$aryloxy, $-(NR^5)_k(CH_2)((C_3-C_{10})$cycloalkyl$)_k(CH_2)_m$aryloxy, $-(NR^5)_k(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_m$aryloxy, $-Z(S(O)_qR^5)$, $-Z($aryl), $-Z($heteroaryl), $-Z((C_3-C_{10})$cycloalkyl), $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$ or $-Z(Q)$ radical; or

X and A together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic carbocyclic or heterocyclic ring which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, $-NH_2$, $-NH((C_1-C_8)$alkyl$)$, $-N((C_1-C_8)$alkyl$)_2$, or (C_1-C_8)alkyl radical;

each R^5 and R^7 are each independently a hydrogen, -OH, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl or (C_3-C_{10})cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 6;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, -Z(COOH), -Z(OH), $-Z(NO_2)$, -Z(SH), $-(C_1-C_8)$alkyl, $-(C_1-C_8)$acyloxy, $-(C_3-C_{10})$cycloalkyl, $-S-((C_1-C_8)alkyl)_k$-aryl, $-((C_1-C_8)alkyl)_k-SO_2NH$-aryl, $-S-(C_1-C_8)$alkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^9SO_2R^9)$, $-Z(CON(R^9)_2)$, $-Z(CO_2R^9)$, $-Z(N(R^9)_2)$, $-Z(NR^9CON(R^9)_2)$, $-Z(NR^9(CO)R^9)$, $-Z(NR^9CO_2R^9)$, $-Z(COR^9)$, $-Z(S(O)_pR^9)$ or -Z(Q), wherein each R^9 is independently a hydrogen or (C_1-C_8)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with 1-3 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_8)alkyl.

3. The compound of claim 2 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N; A is N-H, $N-R^4$ or CHR^4;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_6)cycloalkyl, $-Z((C_1-C_8)alkoxy)$, $-Z((C_3-C_6)cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(N(R^5)_2)$ or -Z(Q) radical;

R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(N(R^5)_2)$, $-Z(NR^{10}CON(R^5)_2)$, $-Z(NR^{10}(CO)R^5)$, $-Z(NR^{10}CO_2R^5)$, $-Z(S(0)_pR^5)$ or -Z(Q) radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_3-C_8)alkyl, $-((C_1-C_8)alkyl)OH$, $(C_1-C_8)alkoxy-(C_1-C_8)alkyl-$, $-((C_1-C_8)alkyl)N(R^5)_2$, $-((C_1-C_8)alkyl)S(0)_p((C_1-C_8)alkyl)$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(0)_pR^5$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(COR^5)$, $-((C_1-C_8)alkyl)(CO_2R^5)$, $-((C_1-C_8)alkyl)(COR^5)$, $-D'(S(0)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl), $-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^{10}SO_2R^5)$, $-D'(CON(R^5)_2)$, $-D'(NR^{10}CON(R^5)_2)$, $-D'(NR^{10}(CO)R^5)$, $-D'(NR^{10}CO_2R^5)$, -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), $-D((C_3-C_{10})cycloalkyl)$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$,

$-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k$-D-Q radical, provided R^3 is not $-SO_2NH_2$;

R^4 is a (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, $-N(R^5)_2$ or -Z(Q) radical;

X is a $-(NR^{10})((C_1-C_8)alkyl)(C_1-C_8)alkoxy$, $-(NR^{10})((C_1-C_8)alkyl)aryloxy$, $-(NR^{10})S(O)_pR^5$, $-(NR^{10})((C_1-C_8)alkyl)S(O)_pR^5$, $-(NR^{10})D(C_1-C_8)alkoxy$, $-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$, $-(NR^{10})(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$, $-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$, $-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)aryloxy$, $-(NR^{10})(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$, $-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_maryloxy$, $-(NR^{10})D(S(O)_qR^5)$, $-(NR^{10})D'(S(O)_qR^5)$, $-(NR^{10})D(aryl)$, $-(NR^{10})D'(aryl)$, $-(NR^{10})D(heteroaryl)$, $-(NR^{10})D'(heteroaryl)$, $-(NR^{10})D((C_3-C_{10})cycloalkyl)$, $-(NR^{10})D'((C_3-C_{10})cycloalkyl)$, $-(NR^{10})D(NR^{10}SO_2R^5)$, $-(NR^{10})D'(NR^{10}SO_2R^5)$, $-(NR^{10})D(CON(R^5)_2)$, $-(NR^{10})D'(CON(R^5)_2)$, $-(NR^{10})D(CO_2R^5)$, $-(NR^{10})D'(CO_2R^5)$, $-(NR^{10})D(N(R^5)_2)$, $-N(R^5)_2$, $-(NR^{10})D'(N(R^5)_2)$, $-(NR^{10})D(NR^{10}CON(R^5)_2)$, $-(NR^{10})D'(NR^{10}CON(R^5)_2)$, $-(NR^{10})D(NR^{10}(CO)R^5)$, $-(NR^{10})D'(NR^{10}(CO)R^5)$, $-(NR^{10})D(NR^{10}CO_2R^5)$, $-(NR^{10})D'(NR^{10}CO_2R^5)$, $-(NR^{10})D(COR^5)$, $-(NR^{10})D'(COR^5)$, $-(NR^{10})$D-Q, $-(NR^{10})$D'-Q or Q radical;

wherein each R^{10} is independently a hydrogen or (C_1-C_4)alkyl radical; or

X and A together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic heterocyclic ring which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or (C_1-C_4)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, (C_1-C_4)alkyl or (C_3-C_6)cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 4;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^1, R^2, R^3, R^4 and R^5 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$acyloxy, $-(C_3-C_6)$cycloalkyl, $-S-((C_1-C_4)alkyl)_k$-aryl, $-((C_1-C_4)alkyl)_k-SO_2NH$-aryl, aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$, $-S(0)_2(C_1-C_4)$alkyl or Q, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with 1-2 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_4)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 0-3.

4. The compound of claim 3 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N; A is N-H or N-R^4;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k$-cyclopropyl or $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-N(R^{10})_2$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-(C_1-C_4)\text{alkoxy})$, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-(CON(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-(N(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-(S(O)_pR^5)$ or $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k$-Q radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)\text{alkyl})OH$, (C_1-C_4)alkoxy-(C_1-C_4)alkyl-, $-((C_1-C_4)\text{alkyl})N(R^5)_2$, $-(CH_2)((C_3-C_6)\text{cycloalkyl})_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})_k(CH_2)OH$, $-(CH_2)((C_3-C_6)\text{cycloalkyl})_k(CH_2)_m(C_1-C_4)$alkoxy, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})(CH_2)_m(C_1-C_4)$alkoxy, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})_k(CH_2)(C_1-C_4)$alkoxy, $-(CH_2)((C_3-C_6)\text{cycloalkyl})_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})(CH_2)_m(COR^5)$, -D'$(S(O)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl), -D'$((C_3-C_{10})$cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), -D$(NR^{10}SO_2R^5)$, -D$(CON(R^5)_2)$, -D$(S(O)_qR^5)$,

$-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-$ Q radical, provided R^3 is not $-SO_2NH_2$;

R^4 is a (C_1-C_4)alkyl radical;

X is a $-(N((C_1-C_4)alkyl))-((C_1-C_4)alkyl)aryloxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$, $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)aryloxy$, $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_maryloxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_maryloxy$, $-(N((C_1-C_4)alkyl))-D(aryl)$, $-(N((C_1-C_4)alkyl))-D'(aryl)$, $-(N((C_1-C_4)alkyl))-D(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D'(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}SO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(N(R^5)_2)$, $-N(R^5)_2$, $-(N((C_1-C_4)alkyl))-D(NR^{10}CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}(CO)R^5)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(COR^5)$, $-(N((C_1-C_4)alkyl))-D-Q$, $-(N((C_1-C_4)alkyl))-D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or (C_1-C_4)alkyl radical; or

X and A together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic heterocyclyl moiety which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH,

halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or (C_1-C_4)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$ or (C_1-C_4)alkyl radical;

D is $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 3;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-3.

5. The compound of claim 4 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N; A is N-H;

R^1 is a bromo, chloro, fluoro, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl, (C_1-C_2)alkoxy, $-(NR^{10})_k((C_1-C_2)alkyl)_k$-cyclopropyl, $-NH_2$ or $-NH((C_1-C_2)alkyl)$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl or (C_1-C_2)alkoxy radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)alkyl)OH$, $(C_1-C_4)alkoxy-(C_1-C_4)alkyl-$, $-((C_1-C_4)alkyl)N(R^5)_2$, $-(CH_2)((C_5-C_6)cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_5-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_2)alkoxy$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_m(C_1-C_2)alkoxy$, $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)(C_1-C_2)alkoxy$, $-(CH_2)((C_5-C_6)cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_m(COR^5)$, -D'($S(O)_qR^5$), -D'(aryloxy), -D'(aryl), -D'(heteroaryl), -D'((C_3-C_6)cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), -D($NR^{10}SO_2R^5$), -D($CON(R^5)_2$), -D($S(O)_qR^5$), -D($NR^{10}CON(R^5)_2$), -D($NR^{10}(CO)R^5$), -D($NR^{10}CO_2R^5$) or $-(NR^{10})_k$-D-Q radical, provided R^3 is not $-SO_2NH_2$;

X is a $-N((C_1-C_4)alkyl)_2$ or 4-membered to 10-membered heterocyclyl or heteroaryl ring, having a nitrogen atom ring member bonded directly to the carbon atom adjoining X, optionally substituted with 1-2 radicals of R^8;

wherein each R^{10} is independently a hydrogen or (C_1-C_2)alkyl radical; or

X and A together with the adjoining carbon atoms form a 8-membered to 10-membered bicyclic heterocyclyl moiety which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$, or (C_1-C_2)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or (C_1-C_2)alkyl radical;

D is $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 2;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_2)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-2.

6. The compound of claim 2 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is $C(R^6)$; A is N-H, N-R^4 or CHR^4;

R^6 is a hydrogen, -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, (C_1-C_4)alkyl or (C_3-C_6)cycloalkyl radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_6)cycloalkyl, $-Z((C_1-C_8)alkoxy)$, $-Z((C_3-C_6)cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(N(R^5)_2)$ or -Z(Q) radical;

R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(N(R^5)_2)$, $-Z(NR^{10}CON(R^5)_2)$, $-Z(NR^{10}(CO)R^5)$, $-Z(NR^{10}CO_2R^5)$, $-Z(S(O)_pR^5)$ or -Z(Q) radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_3-C_8)alkyl, $-((C_1-C_8)alkyl)OH$, $(C_1-C_8)alkoxy-(C_1-C_8)alkyl-$, $-((C_1-C_8)alkyl)N(R^5)_2$, $-((C_1-C_8)alkyl)S(O)_p((C_1-C_8)alkyl)$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$,

$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mN(R^5)_2$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(O)_pR^5$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(CO_2R^5)$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(COR^5)$,
$-((C_1-C_8)alkyl)(CO_2R^5)$, $-((C_1-C_8)alkyl)(COR^5)$,
$-D'(S(O)_qR^5)$, $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$,
$-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^{10}SO_2R^5)$, $-D'(CON(R^5)_2)$,
$-D'(NR^{10}CON(R^5)_2)$, $-D'(NR^{10}(CO)R^5)$, $-D'(NR^{10}CO_2R^5)$, $-D'(Q)$,
$-D(aryloxy)$, $-D(aryl)$, $-D(heteroaryl)$,
$-D((C_3-C_{10})cycloalkyl)$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$,
$-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$
or $-(NR^{10})_k-D-Q$ radical, provided R^3 is not $-SO_2NH_2$;

R^4 is a (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, $-N(R^5)_2$ or $-Z(Q)$ radical;

X is a $-(NR^{10})((C_1-C_8)alkyl)(C_1-C_8)alkoxy$,
$-(NR^{10})((C_1-C_8)alkyl)aryloxy$, $-(NR^{10})S(O)_pR^5$,
$-(NR^{10})((C_1-C_8)alkyl)S(O)_pR^5$, $-(NR^{10})D(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)aryloxy$,
$-(NR^{10})(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_maryloxy$,
$-(NR^{10})D(S(O)_qR^5)$, $-(NR^{10})D'(S(O)_qR^5)$, $-(NR^{10})D(aryl)$,
$-(NR^{10})D'(aryl)$, $-(NR^{10})D(heteroaryl)$,
$-(NR^{10})D'(heteroaryl)$, $-(NR^{10})D((C_3-C_{10})cycloalkyl)$,
$-(NR^{10})D'((C_3-C_{10})cycloalkyl)$, $-(NR^{10})D(NR^{10}SO_2R^5)$,
$-(NR^{10})D'(NR^{10}SO_2R^5)$, $-(NR^{10})D(CON(R^5)_2)$, $-(NR^{10})D'(CON(R^5)_2)$,
$-(NR^{10})D(CO_2R^5)$, $-(NR^{10})D'(CO_2R^5)$, $-(NR^{10})D(N(R^5)_2)$, $-N(R^5)_2$,
$-(NR^{10})D'(N(R^5)_2)$, $-(NR^{10})D(NR^{10}CON(R^5)_2)$,
$-(NR^{10})D'(NR^{10}CON(R^5)_2)$, $-(NR^{10})D(NR^{10}(CO)R^5)$,
$-(NR^{10})D'(NR^{10}(CO)R^5)$, $-(NR^{10})D(NR^{10}CO_2R^5)$,

$-(NR^{10})D'(NR^{10}CO_2R^5)$, $-(NR^{10})D(COR^5)$, $-(NR^{10})D'(COR^5)$, $-(NR^{10})D-Q$, $-(NR^{10})D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or (C_1-C_4)alkyl radical; or

X and A together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic heterocyclic ring which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or (C_1-C_4)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, (C_1-C_4)alkyl or (C_3-C_6)cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 4;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^1, R^2, R^3, R^4, R^5 and R^6 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$acyloxy, $-(C_3-C_6)$cycloalkyl,

$-S-((C_1-C_4)alkyl)_k-aryl$, $-((C_1-C_4)alkyl)_k-SO_2NH-aryl$, aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$, $-S(O)_2(C_1-C_4)alkyl$ or Q, wherein each R^9 is independently a hydrogen or $(C_1-C_4)alkyl$ radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with 1-2 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or $(C_1-C_4)alkyl$; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 0-3.

7. The compound of claim 6 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is $C(R^6)$; A is N-H, $N-R^4$;

R^6 is a hydrogen, -OH, chloro, fluoro, $-CF_3$, $-OCF_3$, $(C_1-C_2)alkoxy$, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or $(C_1-C_4)alkyl$ radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, $(C_1-C_4)alkyl$, $(C_1-C_4)alkoxy$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-$ cyclopropyl or $-(NR^{10})_k((C_1-C_2)alkyl)_k-N(R^{10})_2$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, $(C_1-C_4)alkyl$, $(C_3-C_6)cycloalkyl$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(C_1-C_4)alkoxy)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(CON(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(N(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(S(O)_pR^5)$ or $-(NR^{10})_k((C_1-C_2)alkyl)_k-Q$ radical;

R^3 is a $(C_3-C_6)cycloalkyl$, $(C_3-C_6)alkyl$, $-((C_1-C_4)alkyl)OH$, $(C_1-C_4)alkoxy-(C_1-C_4)alkyl-$, $-((C_1-C_4)alkyl)N(R^5)_2$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_mOH$,

$-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mOH$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)OH$,
$-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$,
$-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_mN(R^5)_2$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mN(R^5)_2$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)N(R^5)_2$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mS(O)_pR^5$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(CO_2R^5)$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(COR^5)$, -D'($S(O)_qR^5$),
-D'(aryloxy), -D'(aryl), -D'(heteroaryl),
-D'((C_3-C_{10})cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl),
-D(heteroaryl), -D($NR^{10}SO_2R^5$), -D($CON(R^5)_2$), -D($S(O)_qR^5$),
-D($NR^{10}CON(R^5)_2$), -D($NR^{10}(CO)R^5$), -D($NR^{10}CO_2R^5$) or -$(NR^{10})_k$-D-Q radical, provided R^3 is not $-SO_2NH_2$;

R^4 is a (C_1-C_4)alkyl radical;

X is a -(N((C_1-C_4)alkyl))-((C_1-C_4)alkyl)aryloxy,
-(N((C_1-C_4)alkyl))-
$(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$,
-(N((C_1-C_4)alkyl))-
$(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$,
-(N((C_1-C_4)alkyl))-
$(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$,
-(N((C_1-C_4)alkyl))-$(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)$aryloxy,
-(N((C_1-C_4)alkyl))-$(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m$aryloxy,
-(N((C_1-C_4)alkyl))-$(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m$aryloxy,
-(N((C_1-C_4)alkyl))-D(aryl), -(N((C_1-C_4)alkyl))-D'(aryl),
-(N((C_1-C_4)alkyl))-D(heteroaryl), -(N((C_1-C_4)alkyl))-
D'(heteroaryl), -(N((C_1-C_4)alkyl))-D($NR^{10}SO_2R^5$),
-(N((C_1-C_4)alkyl))-D($CON(R^5)_2$), -(N((C_1-C_4)alkyl))-
D(CO_2R^5), -(N((C_1-C_4)alkyl))-D($N(R^5)_2$), -$N(R^5)_2$,
-(N((C_1-C_4)alkyl))-D($NR^{10}CON(R^5)_2$), -(N((C_1-C_4)alkyl))-
D($NR^{10}(CO)R^5$), -(N((C_1-C_4)alkyl))-D($NR^{10}CO_2R^5$),

$-(N((C_1-C_4)alkyl))-D(COR^5)$, $-(N((C_1-C_4)alkyl))-D-Q$, $-(N((C_1-C_4)alkyl))-D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or (C_1-C_4)alkyl radical; or

X and A together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic heterocyclyl moiety which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or (C_1-C_4)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$ or (C_1-C_4)alkyl radical;

D is $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 3;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2, and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or

$-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-3.

8. The compound of claim 7 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is $C(R^6)$; A is N-H;

R^6 is a hydrogen, -OH, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy or (C_1-C_2)alkyl radical;

R^1 is a bromo, chloro, fluoro, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl, (C_1-C_2)alkoxy, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k$-cyclopropyl, $-NH_2$ or $-NH((C_1-C_2)\text{alkyl})$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl or (C_1-C_2)alkoxy radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl,
$-((C_1-C_4)\text{alkyl})OH$, (C_1-C_4)alkoxy-(C_1-C_4)alkyl-,
$-((C_1-C_4)\text{alkyl})N(R^5)_2$, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_mOH$,
$-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mOH$,
$-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)OH$,
$-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_m(C_1-C_2)$alkoxy,
$-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(C_1-C_2)$alkoxy,
$-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)(C_1-C_2)$alkoxy,
$-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_mN(R^5)_2$,
$-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mN(R^5)_2$,
$-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)N(R^5)_2$,
$-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mS(0)_pR^5$,
$-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(CO_2R^5)$,
$-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$,

-D'(aryloxy), -D'(aryl), -D'(heteroaryl), -D'((C_3-C_6)cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), -D($NR^{10}SO_2R^5$), -D($CON(R^5)_2$), -D($S(O)_qR^5$), -D($NR^{10}CON(R^5)_2$), -D($NR^{10}(CO)R^5$), -D($NR^{10}CO_2R^5$) or -$(NR^{10})_k$-D-Q radical, provided R^3 is not $-SO_2NH_2$;

X is a -N((C_1-C_4)alkyl)$_2$ or 4-membered to 10-membered heterocyclyl or heteroaryl ring, having a nitrogen atom ring member bonded directly to the carbon atom adjoining X, optionally substituted with 1-2 radicals of R^8;

wherein each R^{10} is independently a hydrogen or (C_1-C_2)alkyl radical; or

X and A together with the adjoining carbon atoms form a 8-membered to 10-membered bicyclic heterocyclyl moiety which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy, $-NH_2$, -NH((C_1-C_2)alkyl), -N((C_1-C_2)alkyl)$_2$, or (C_1-C_2)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_2)alkoxy, $-NH_2$, -NH((C_1-C_2)alkyl), -N((C_1-C_2)alkyl)$_2$ or (C_1-C_2)alkyl radical;

D is -$(CH_2)_m$((C_5-C_6)cycloalkyl)$_k$$(CH_2)_m$- and D' is -(($C_1$-$C_4$)alkyl)$_k$-;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 2;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_2)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-2.

9. The compound of claim 1 which is:

2-Methyl-6-phenyl-4-(2-1,2,3,4-tetrahydroquinolino-2-yl)pyrrolo[3,2-d]pyrimidine;

(S)-[1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl) pyrrolidin-2-yl]methan-1-ol;

1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl) pyrrolidin-3-ol;

4-Homopiperidyl-2-methyl-6-phenylpyrrolo[3,2-d] pyrimidine;

2-Methyl-6-phenyl-4-pyrrolidinylpyrrolo[3,2-d] pyrimidine;

2-Methyl-6-(4-methylphenyl)-4-piperidylpyrrolo[3,2-d] pyrimidine;

Dimethyl[1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(4-piperidyl)]amine;

Dimethyl{[1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(2-piperidyl)]methyl}amine;

2-Isopropyl-6-phenyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

cis/trans-4-(3,5-dimethylpiperidinyl)-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine;

[1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)-3-piperidyl]methan-1-ol;

2,5-Dimethyl-6-phenyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

2-(3-Hydroxyphenyl)-7-piperidylpyrrolo[3,2-b]pyridine;

7-Piperidyl-2-(2-pyridyl)pyrrolo[3,2-b]pyridine;

2-Cyclohex-1-enyl-7-piperidylpyrrolo[3,2-b]pyridine Hydrochloride;

2-Cyclohexyl-7-piperidylpyrrolo[3,2-b]pyridine;

2-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)thiophene;

2-Methyl-6-phenyl-4-(3-pyridinyl)pyrrolo[3,2-d]pyrimidine;

2-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin4-yl)-1,3-thiazole;

2-Methyl-4-(2-methylpyrrolidin-1-yl)-6-phenylpyrrolo [3,2-d]pyrimidine;

2-Methyl-6-phenyl-4-(pyrrolinyl)pyrrolo[3,2-d] pyrimidine;

2-Methyl-6-phenyl-4-(2-piperidineethanolyl)pyrrolo [3,2-d]pyrimidine;

2-Methyl-6-phenyl-4-(2-methylpiperidinyl)pyrrolo[3,2-d] pyrimidine;

2-Methyl-6-phenyl-4-(2-ethylpiperidinyl)pyrrolo[3,2-d] pyrimidine;

2-Methyl-6-phenyl-4-(1,2,3,6-tetrahydropyridinyl) pyrrolo[3,2-d]pyrimidine;

6-Phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine-2-ylamine;

2-Methylthio-6-phenyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

2-Ethyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine;

2-Cyclopropyl-6-phenyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

6-(3-Chlorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

4-Methoxy-1-(2-methyl-4-piperidylpyrrolo[4,5-d] pyrimidin-6-yl)benzene;

4-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl) phenol;

6-(4-Fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

4-Azetidinyl-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine;

2-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl) thiophene;

2-Methyl-4-piperidyl-6-(2-pyridyl)pyrrolo[3,2-d] pyrimidine;

6-Adamantanyl-2-methyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

2-Methyl-4-piperidyl-6-pyrazin-2-ylpyrrolo[3,2-d] pyrimidine;

2-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl) benzo[b]furan;

2,7-Dimethyl-6-phenyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

6-Phenyl-4-piperidyl-2-(trifluoromethyl)pyrrolo[3,2-d] pyrimidine;

6-(4-Chlorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

(6-Phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine-2-yl) propylamine;

6-(*tert*-Butyl)-2-methyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

2-Methyl-6-(2-methylcyclopent-1-eneyl)-4-piperidyl pyrrolo[3,2-d]pyrimidine;

2,5-Dimethyl-3-(2-methyl-4-piperidylpyrrolo[4,5-d] pyrimidin-6-yl)thiophene;

2-Methyl-6-(4-phenylphenyl)-4-piperidylpyrrolo[3,2-d] pyrimidine;

3-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)-1-(phenylsulfonyl)pyrrole;

6-(2-Fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

6-(3-Fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d] pyrimidine;

2-Methyl-6-phenyl-4-(4-phenylpiperazinyl)pyrrolo[3,2-*d*] pyrimidine;

2-Methyl-4-piperidyl-6-(3-(trifluoromethyl)phenyl) pyrrolo[3,2-*d*]pyrimidine;

6-(2,6-Difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

6-(2,5-Difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

2-Methyl-4-piperidyl-6-(4-(trifluoromethyl)phenyl) pyrrolo[3,2-*d*]pyrimidine;

2-Methyl-4-piperidyl-6-(2,3,4-trichlorophenyl) pyrrolo[3,2-*d*]pyrimidine;

5-[2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]-2*H*-benzo[*d*]1,3-dioxolane;

2-Methyl-4-piperidyl-6-(3,4,5-trifluorophenyl) pyrrolo[3,2-*d*]pyrimidine;

6-(3,5-Difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

6-(3,4-Dichlorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

2-Fluoro-1-methoxy-4-[2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]benzene;

2-Fluoro-4-[2-methyl-4-pyridylpyrrolo[4,5-*d*]pyrimidin-6-yl]phenol;

6-((3,5-bis(Trifluoromethyl)phenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

Trifluoro[4-(2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl)phenylthio]methane;

6-(3,4-Dimethylphenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

6-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)-2*H*,3*H*-benzo[*e*]1,4-dioxane;

1,2-Dimethoxy-4-(2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl)benzene;

6-Fluoren-2-yl-2-methyl-4-piperidylpyrrolo[3,2-*d*] pyrimidine;

2-Methyl-4-piperidyl-6-(2-5,6,7,8-tetrahydronaphthyl) pyrrolo[3,2-*d*]pyrimidine;

2-Methyl-6-(5-methyl-1-phenylpyrazol-4-yl)-4-piperidyl pyrrolo[3,2-*d*]pyrimidine;

6-Indan-5-yl-2-methyl-4-piperidylpyrrolo[3,2-*d*] pyrimidine;

5-[2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]-2,3-dihydrobenzo[*b*]furan;

2,4-Dimethyl-5-[2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl]-1,3-thiazole;

2,7-Dimethyl-4-piperidyl-6-((4-trifluoromethyl)phenyl) pyrrolo[3,2-*d*]pyrimidine;

6-(4-Fluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

6-(3,4-Dichlorophenyl)-2,7-dimethyl-4-piperidyl pyrrolo[3,2-*d*]pyrimidine;

1-(2,7-Dimethyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)-4-methoxybenzene;

4-(2,7-Dimethyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenol;

6-(3,5-Difluorophenyl)-2,7-dimethyl-4-piperidyl pyrrolo[3,2-*d*]pyrimidine;

1-(2,7-Dimethyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)-3-methoxybenzene;

4-(6-(3,4-Difluorophenyl)-2-methylpyrrolo[2,3-*e*] pyrimidin-4-yl)morpholine;

1-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)-4-(methylsulfonyl)benzene;

1,2,3-Trimethoxy-5-(2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl)benzene;

7-Ethyl-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

5-(3-Chloro-4-fluorophenyl)-2-(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)furan;

6-(4-Fluorophenyl)-2-methyl-4-(2-methylpiperidyl) pyrrolo[3,2-*d*]pyrimidine;

6-Butyl-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

2,6-Dimethyl-4-piperidyl-7-propylpyrrolo[3,2-*d*] pyrimidine;

1-(4-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenyl)ethan-1-one;

2-Methyl-6-(4-(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenyl)-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

7-Fluoro-2-methyl-6-piperidylpyrrolo[3,2-*d*]pyrimidine;

2-Methyl-6-phenyl-4-piperidyl-7-pyrrolidinyl pyrrolo[3,2-*d*]pyrimidine;

3-Methyl-2-(2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl)benzo[*b*]thiophene;

4-Chloro-1-(((2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)methyl)sulfonyl)benzene;

4-Methoxy-1-((2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)methyl)benzene;

1-(2,6-Dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-7-yl)-4-methoxybenzene;

2-Methyl-6-(2-naphthyl)-4-piperidylpyrrolo[3,2-*d*] pyrimidine;

3,5-Dimethyl-2-(2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl)benzo[*b*]thiophene;

7-Methoxy-2-(2-methyl-4-piperidylpyrrolo[4,5-*d*] pyrimidin-6-yl)benzo[*b*]furan;

6-((4-Fluorophenyl)methyl)-2-methyl-4-piperidyl pyrrolo[3,2-*d*]pyrimidine;

7-(4-Fluorophenyl)-2,6-dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

((2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)methoxy)benzene;

2,6-Dimethyl-7-phenoxy-4-piperidylpyrrolo[3,2-*d*] pyrimidine;

2-Methyl-6-(2-phenylethyl)-4-piperidylpyrrolo[3,2-*d*] pyrimidine;

2,6-Dimethyl-7-benzyl-4-piperidylpyrrolo[3,2-*d*] pyrimidine;

5-(2,7-Dimethyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)-2*H*-benzo[*d*]1,3-dioxolane;

6-(3,4-Difluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl) piperidin-3-ol;

1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl) piperidin-4-ol;

8-Aza-8-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl)-1,4-dioxaspiro[4,5]decane;

1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl)-4-(3-(trifluoromethyl)phenyl)piperidin-4-ol;

1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl) piperidin-2-one;

2-Methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-1-ol;

4-((6*S*,2*R*)-2,6-Dimethyl)-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine;

4-((6*S*,2*R*)-2,6-Dimethylpiperidyl)-6-(4-fluorophenyl)-2-methylpyrrolo[3,2-*d*]pyridine;

3-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl) phenylamine;

4-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl) phenylamine;

1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)-4-naphthylsulfonyl)piperazine;

2-Methyl-6-phenyl-4-pyrrolidinylpyrrolo[3,2-*d*] pyrimidine;

Trifluoro(4-(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenoxy)methane;

6-Phenyl-4-piperidyl-2-propylpyrrolo[3,2-*d*]pyrimidine;

2-Methyl-4-(3-pyrrolinyl)-6-(3-(trifluoromethyl)phenyl)pyrrolo[3,2-*d*]pyrimidine;

6-(3-Chlorophenyl)-2-methyl-4-(3-pyrrolinyl)pyrrolo[3,2-*d*]pyrimidine;

6-(4-Fluorophenyl)-2-methyl-4-(3-pyrrolinyl)pyrrolo[3,2-*d*]pyrimidine;

6-Phenyl-4-piperidyl)pyrrolo[3,2-d]pyrimidine-2-yl hydroxylamine;

6-(3,4-Dichlorophenyl)-2-methyl-4-(3-pyrrolinyl)pyrrolo[3,2-*d*]pyrimidine;

2-(2-Methylpropyl)-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

2-Ethyl-6-phenyl-4-(2-1,2,3,4-tetrahydroisoquinolyl)pyrrolo[3,2-*d*]pyrimidine;

2-Chloro-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

Dimethyl(6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-2-yl)amine;

2-Methoxy-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

Methyl(6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-2-yl)amine;

6-Phenyl-2-(4-phenylpiperazinyl)-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

2-Cyclopropyl-6-(4-fluorophenyl)-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

4-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenyl 2,2-dimethylpropanoate;

7-Bromo-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;

4-(8-azabicyclo[3.2.1]oct-8-yl)-2-methyl-6-phenyl pyrrolo[3,2-*d*]pyrimidine;

(1-[2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)-2-piperidyl)methan-1-ol;

4-Indolinyl-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine;

2-Methyl-6-phenyl-4-pyrazolypyrrolo[3,2-*d*]pyrimidine;

2-Methyl-6-phenyl-4-[1,2,4-triazolyl]pyrrolo[3,2-*d*]pyrimidine;

4-(2,5-Dimethyl(3-pyrrolinyl)-2-methyl-6-phenyl pyrrolo[3,2-*d*]pyrimidine;

1-(2-Furanylcarbonyl)-4-(2-methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)piperazine;

1-Acetyl-4-(2-methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)piperazine;

1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)-4-(methylsulfonyl)piperazine;

1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl(phenylsulfonyl)piperazine;

2-Methyl-5-phenyl-7,7a,8,9,10,11-hexahydro-1,3,11a-triaza-pyrrolo[3,2,1-de]phenanthridine;

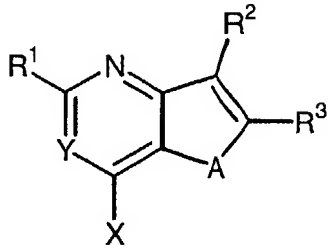
5-Methyl-2-(4-fluorophenyl)-7-piperidylpyrrolo[3,2-b]pyridine;

(7-Aminoheptyl)-(6-phenyl-4-piperidylpyrrolo[3,2-d] pyrimidin-2-yl)amine; or

(4-Aminobutyl)-(6-phenyl-4-piperidylpyrrolo[3,2-d] pyrimidin-2-yl)amine; or

a pharmaceutically acceptable salt thereof.

10. A compound of formula



or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N or C(R^6); A is S, S(O), $S(O)_2$ or O;

R^6 is a hydrogen, -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl or -Z(Q) radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$,

-Z(CO_2R^5), -Z($N(R^5)_2$), -Z($NR^5CON(R^5)_2$), -Z($NR^5(CO)R^5$), -Z($NR^5CO_2R^5$), -Z(COR^5), -Z($S(O)_pR^5$) or -Z(Q) radical;

R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, -Z((C_1-C_8)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C_3-C_{10})cycloalkyl), -Z($NR^5SO_2R^5$), -Z($CON(R^5)_2$), -Z(CO_2R^5), -Z($N(R^5)_2$), -Z($NR^5CON(R^5)_2$), -Z($NR^5(CO)R^5$), -Z($NR^5CO_2R^5$), -Z(COR^5), -Z($S(O)_pR^5$) or -Z(Q) radical, provided that R^2 is not an optionally substituted phenyl, pyridyl, pyrazinyl, pyrimidyl or pyridazinyl radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_1-C_8)alkyl, -((C_1-C_8)alkyl)OH, (C_1-C_8)alkoxy-(C_1-C_8)alkyl-, -((C_1-C_8)alkyl)$N(R^5)_2$, -((C_1-C_8)alkyl)$S(O)_p$((C_1-C_8)alkyl), -(CH_2)((C_3-C_{10})cycloalkyl)$_k(CH_2)_m$OH, -$(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_m$OH, -$(CH_2)_m$((C_3-C_{10})cycloalkyl)$_k(CH_2)$OH, -(CH_2)((C_3-C_{10})cycloalkyl)$_k(CH_2)_m$(C_1-C_8)alkoxy, -$(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_m$(C_1-C_8)alkoxy, -$(CH_2)_m$((C_3-C_{10})cycloalkyl)$_k(CH_2)$(C_1-C_8)alkoxy, -(CH_2)((C_3-C_{10})cycloalkyl)$_k(CH_2)_mN(R^5)_2$, -$(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_mN(R^5)_2$, -$(CH_2)_m$((C_3-C_{10})cycloalkyl)$_k(CH_2)N(R^5)_2$, -$(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_mS(O)_pR^5$, -D'($S(O)_qR^5$), -D'(aryloxy), -D'(aryl), -D'(heteroaryl), -D'((C_3-C_{10})cycloalkyl), -D'($NR^5SO_2R^5$), -D'($CON(R^5)_2$), -D'(CO_2R^5), -D'($NR^5CON(R^5)_2$), -D'($NR^5(CO)R^5$), -D'($NR^5CO_2R^5$), -D'(COR^5), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), -D((C_3-C_{10})cycloalkyl), -D($NR^5SO_2R^5$), -D($CON(R^5)_2$), -D(CO_2R^5), -D($S(O)_qR^5$), -D($NR^5CON(R^5)_2$), -D($NR^5(CO)R^5$), -D($NR^5CO_2R^5$), -D(COR^5) or -$(NR^5)_k$-D-Q radical;

X is a (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-(NR^5)_k((C_1-C_8)alkyl)(C_1-C_8)alkoxy$, $-(NR^5)_k((C_1-C_8)alkyl)aryloxy$, $-(NR^5)((C_1-C_8)alkyl)_kS(0)_pR^5$, $-(NR^5)_k((C_1-C_8)alkyl)S(0)_pR^5$, $-(NR^5)D(C_1-C_8)alkoxy$, $-(NR^5)(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$, $-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$, $-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$, $-(NR^5)(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)aryloxy$, $-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$, $-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_maryloxy$, $-Z(S(0)_qR^5)$, -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$ or -Z(Q) radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, or (C_1-C_8)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl or (C_3-C_{10})cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 6;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1, R^2, R^3, R^5, R^6 and R^8 is optionally substituted with one or more radicals of halo, $-CF_3$, $-OCF_3$, $-Z(COOH)$, $-Z(OH)$, $-Z(NO_2)$, $-Z(SH)$, $-(C_1-C_8)$alkyl, $-(C_1-C_8)$acyloxy, $-(C_3-C_{10})$cycloalkyl, $-S-((C_1-C_8)alkyl)_k$-aryl, $-((C_1-C_8)alkyl)_k-SO_2NH$-aryl, $-S-(C_1-C_8)$alkyl, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^9SO_2R^9)$, $-Z(CON(R^9)_2)$, $-Z(CO_2R^9)$, $-Z(N(R^9)_2)$, $-Z(NR^9CON(R^9)_2)$, $-Z(NR^9(CO)R^9)$, $-Z(NR^9CO_2R^9)$, $-Z(COR^9)$, $-Z(S(O)_pR^9)$ or $-Z(Q)$, wherein each R^9 is independently a hydrogen or (C_1-C_8)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with one or more radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_8)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 0-4; and

provided that:

(a) when A is S, Y is N, R^2 is H , R^3 is methyl or phenyl and R^1 is phenyl, NH_2, piperazinyl or methyl, then X is not NH_2, morpholinyl, 1-oxidothiomorpholinyl or thiomorpholinyl;

(b) when A is O, Y is C-H, R^1 is H, R^2 is H and R^3 is propyl, butyl or hydroxypropyl, then X is not methyl, benzyl or methoxyphenyl-CH_2-;

(c) when A is S, Y is N, R^2 is H or alkyl, R^3 is methyl, then R^1 is not nitro-furyl, $-NH-(C_2-C_{10})alkyl-NH_2$, $-N(alkyl)-(C_2-C_{10})alkyl-NH_2$ or -N(methyl)-ethyl-$NHSO_2$-tolyl;

(d) when A is S, Y is N, R^2 is H, halo, $-NO_2$ or alkyl, R^3 is alkyl or phenyl and X is Q, -N(alkyl-OH)2,

-N(methyl)-ethyl-S-methyl or -N(methyl)-ethyl-S(O)-methyl, then R^1 is not Q, -N(alkyl-OH)2, -N(methyl)-ethyl-S-methyl or -N(methyl)-ethyl-S(O)-methyl;

(e) when A is O or S, Y is CH, R^1 is H and R^2 is H, then R^3 is not $-SO_2NH_2$;

(f) when A is S, Y is N, R^1 is H and R^2 is H, then (1) when R^3 is phenyl, X is not $-NH-NH_2$, optionally substituted indolylalkylamino, optionally substituted indolylamino, optionally substituted thiazolidinonylamino or optionally substituted azetidinonylamino, and (2) when R^3 is methyl, X is not piperidinyl; and

(g) when A is O, Y is N, R^1 is optionally substituted phenyl, R^2 is H and R^3 is alkyl, then X is not optionally substituted phenyl.

11. The compound of claim 10 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N or $C(R^6)$; A is S, S(O), $S(O)_2$ or O;

R^6 is a hydrogen, -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl or -Z(Q) radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or -Z(Q) radical, provided R^1 is not an optionally substituted aryl or heteroaryl radical;

R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, -Z((C_1-C_8)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C_3-C_{10})cycloalkyl), -Z($NR^5SO_2R^5$), -Z($CON(R^5)_2$), -Z($N(R^5)_2$), -Z($NR^5CON(R^5)_2$), -Z($NR^5(CO)R^5$), -Z($NR^5CO_2R^5$), -Z($S(O)_pR^5$) or -Z(Q) radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_3-C_8)alkyl, -((C_1-C_8)alkyl)OH, (C_1-C_8)alkoxy-(C_1-C_8)alkyl-, -((C_1-C_8)alkyl)$N(R^5)_2$, -((C_1-C_8)alkyl)$S(O)_p$((C_1-C_8)alkyl), $-(CH_2)$((C_3-C_{10})cycloalkyl)$_k(CH_2)_mOH$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_mOH$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$_k(CH_2)$OH, $-(CH_2)$((C_3-C_{10})cycloalkyl)$_k(CH_2)_m(C_1-C_8)$alkoxy, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_m(C_1-C_8)$alkoxy, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$_k(CH_2)(C_1-C_8)$alkoxy, $-(CH_2)$((C_3-C_{10})cycloalkyl)$_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_mN(R^5)_2$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$_k(CH_2)N(R^5)_2$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_mS(O)_pR^5$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_m(CO_2R^5)$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_m(COR^5)$, -((C_1-C_8)alkyl)(CO_2R^5), -((C_1-C_8)alkyl)(COR^5), -D'($S(O)_qR^5$), -D'(aryloxy), -D'(aryl), -D'(heteroaryl), -D'((C_3-C_{10})cycloalkyl), -D'($NR^5SO_2R^5$), -D'($CON(R^5)_2$), -D'($NR^5CON(R^5)_2$), -D'($NR^5(CO)R^5$), -D'($NR^5CO_2R^5$), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), -D((C_3-C_{10})cycloalkyl), -D($NR^5SO_2R^5$), -D($CON(R^5)_2$), -D($S(O)_qR^5$), -D($NR^5CON(R^5)_2$), -D($NR^5(CO)R^5$), -D($NR^5CO_2R^5$) or $-(NR^5)_k$-D-Q radical, provided R^3 is not $-SO_2NH_2$;

X is a $-(NR^5)_k$((C_1-C_8)alkyl)(C_1-C_8)alkoxy, $-(NR^5)_k$((C_1-C_8)alkyl)aryloxy, $-(NR^5)$((C_1-C_8)alkyl)$_kS(O)_pR^5$, $-(NR^5)_k$((C_1-C_8)alkyl)$S(O)_pR^5$, $-(NR^5)D(C_1-C_8)$alkoxy, $-(NR^5)(CH_2)_m$((C_3-C_{10})cycloalkyl)$_k(CH_2)(C_1-C_8)$alkoxy,

$-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^5)(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)aryloxy$,
$-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$,
$-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_maryloxy$, $-Z(S(0)_qR^5)$,
$-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$,
$-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$,
$-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$ or
$-Z(Q)$ radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, $(C_1-C_8)alkoxy$, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, or $(C_1-C_8)alkyl$ radical;

each R^5 is independently a hydrogen, -OH, $(C_1-C_8)alkoxy$, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, $(C_1-C_8)alkyl$ or $(C_3-C_{10})cycloalkyl$ radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 6;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1, R^2, R^3, R^5 and R^6 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-Z(COOH)$, $-Z(OH)$, $-Z(NO_2)$, $-Z(SH)$, $-(C_1-C_8)alkyl$, $-(C_1-C_8)acyloxy$, $-(C_3-C_{10})cycloalkyl$, $-S-((C_1-C_8)alkyl)_k-aryl$,

$-((C_1-C_8)alkyl)_k-SO_2NH-aryl$, $-S-(C_1-C_8)alkyl$, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^9SO_2R^9)$, $-Z(CON(R^9)_2)$, $-Z(CO_2R^9)$, $-Z(N(R^9)_2)$, $-Z(NR^9CON(R^9)_2)$, $-Z(NR^9(CO)R^9)$, $-Z(NR^9CO_2R^9)$, $-Z(COR^9)$, $-Z(S(0)_pR^9)$ or $-Z(Q)$, wherein each R^9 is independently a hydrogen or $(C_1-C_8)alkyl$ radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with 1-3 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or $(C_1-C_8)alkyl$.

12. The compound of claim 11 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N; A is S, $S(O)_2$ or O;

R^1 is a hydrogen, halo, $-OH$, $-NO_2$, $-NHOH$, $-CF_3$, $-OCF_3$, $(C_1-C_8)alkyl$, $(C_3-C_6)cycloalkyl$, $-Z((C_1-C_8)alkoxy)$, $-Z((C_3-C_6)cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(N(R^5)_2)$ or $-Z(Q)$ radical;

R^2 is a hydrogen, halo, $-OH$, $-NO_2$, $-CF_3$, $-OCF_3$, $(C_1-C_8)alkyl$, $(C_3-C_{10})cycloalkyl$, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(N(R^5)_2)$, $-Z(NR^{10}CON(R^5)_2)$, $-Z(NR^{10}(CO)R^5)$, $-Z(NR^{10}CO_2R^5)$, $-Z(S(0)_pR^5)$ or $-Z(Q)$ radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a $(C_3-C_{10})cycloalkyl$, $(C_3-C_8)alkyl$, $-((C_1-C_8)alkyl)OH$, $(C_1-C_8)alkoxy-(C_1-C_8)alkyl-$, $-((C_1-C_8)alkyl)N(R^5)_2$, $-((C_1-C_8)alkyl)S(0)_p((C_1-C_8)alkyl)$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,

$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$,
$-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mN(R^5)_2$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(O)_pR^5$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(CO_2R^5)$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(COR^5)$,
$-((C_1-C_8)alkyl)(CO_2R^5)$, $-((C_1-C_8)alkyl)(COR^5)$,
$-D'(S(O)_qR^5)$, $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$,
$-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^{10}SO_2R^5)$, $-D'(CON(R^5)_2)$,
$-D'(NR^{10}CON(R^5)_2)$, $-D'(NR^{10}(CO)R^5)$, $-D'(NR^{10}CO_2R^5)$, $-D'(Q)$,
$-D(aryloxy)$, $-D(aryl)$, $-D(heteroaryl)$,
$-D((C_3-C_{10})cycloalkyl)$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$,
$-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$
or $-(NR^{10})_k$-D—Q radical, provided R^3 is not $-SO_2NH_2$;

X is a $-(NR^{10})((C_1-C_8)alkyl)(C_1-C_8)alkoxy$,
$-(NR^{10})((C_1-C_8)alkyl)aryloxy$, $-(NR^{10})S(O)_pR^5$,
$-(NR^{10})((C_1-C_8)alkyl)S(O)_pR^5$, $-(NR^{10})D(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)aryloxy$,
$-(NR^{10})(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_maryloxy$,
$-(NR^{10})D(S(O)_qR^5)$, $-(NR^{10})D'(S(O)_qR^5)$, $-(NR^{10})D(aryl)$,
$-(NR^{10})D'(aryl)$, $-(NR^{10})D(heteroaryl)$,
$-(NR^{10})D'(heteroaryl)$, $-(NR^{10})D((C_3-C_{10})cycloalkyl)$,
$-(NR^{10})D'((C_3-C_{10})cycloalkyl)$, $-(NR^{10})D(NR^{10}SO_2R^5)$,
$-(NR^{10})D'(NR^{10}SO_2R^5)$, $-(NR^{10})D(CON(R^5)_2)$, $-(NR^{10})D'(CON(R^5)_2)$,
$-(NR^{10})D(CO_2R^5)$, $-(NR^{10})D'(CO_2R^5)$, $-(NR^{10})D(N(R^5)_2)$, $-N(R^5)_2$,
$-(NR^{10})D'(N(R^5)_2)$, $-(NR^{10})D(NR^{10}CON(R^5)_2)$,
$-(NR^{10})D'(NR^{10}CON(R^5)_2)$, $-(NR^{10})D(NR^{10}(CO)R^5)$,
$-(NR^{10})D'(NR^{10}(CO)R^5)$, $-(NR^{10})D(NR^{10}CO_2R^5)$,

$-(NR^{10})D'(NR^{10}CO_2R^5)$, $-(NR^{10})D(COR^5)$, $-(NR^{10})D'(COR^5)$, $-(NR^{10})D-Q$, $-(NR^{10})D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or (C_1-C_4)alkyl radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or (C_1-C_4)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, (C_1-C_4)alkyl or (C_3-C_6)cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 4;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^1, R^2, R^3 and R^5 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$acyloxy, $-(C_3-C_6)$cycloalkyl, $-S-((C_1-C_4)alkyl)_k-aryl$, $-((C_1-C_4)alkyl)_k-SO_2NH-aryl$, aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$, $-S(0)_2(C_1-C_4)$alkyl or Q, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical and wherein such

aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with 1-2 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_4)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 0-3.

13. The compound of claim 12 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N; A is S or O;

R^1 is a hydrogen, halo, $-OH$, $-NO_2$, $-NHOH$, $-CF_3$, $-OCF_3$, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-$cyclopropyl or $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-N(R^{10})_2$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-(C_1-C_4)\text{alkoxy})$, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-(CON(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-(N(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-(S(O)_pR^5)$ or $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-Q$ radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)\text{alkyl})OH$, $(C_1-C_4)\text{alkoxy}-(C_1-C_4)\text{alkyl}-$, $-((C_1-C_4)\text{alkyl})N(R^5)_2$, $-(CH_2)((C_3-C_6)\text{cycloalkyl})_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})_k(CH_2)OH$, $-(CH_2)((C_3-C_6)\text{cycloalkyl})_k(CH_2)_m(C_1-C_4)\text{alkoxy}$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})(CH_2)_m(C_1-C_4)\text{alkoxy}$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})_k(CH_2)(C_1-C_4)\text{alkoxy}$, $-(CH_2)((C_3-C_6)\text{cycloalkyl})_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})(CH_2)_mS(O)_pR^5$,

$-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$, $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$, $-D'((C_3-C_{10})cycloalkyl)$, $-D'(Q)$, $-D(aryloxy)$, $-D(aryl)$, $-D(heteroaryl)$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-$ Q radical, provided R^3 is not $-SO_2NH_2$;

X is a $-(N((C_1-C_4)alkyl))-((C_1-C_4)alkyl)aryloxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$, $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)aryloxy$, $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_maryloxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_maryloxy$, $-(N((C_1-C_4)alkyl))-D(aryl)$, $-(N((C_1-C_4)alkyl))-D'(aryl)$, $-(N((C_1-C_4)alkyl))-D(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D'(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}SO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(N(R^5)_2)$, $-N(R^5)_2$, $-(N((C_1-C_4)alkyl))-D(NR^{10}CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}(CO)R^5)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(COR^5)$, $-(N((C_1-C_4)alkyl))-D-Q$, $-(N((C_1-C_4)alkyl))-D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or $(C_1-C_4)alkyl$ radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, $(C_1-C_4)alkoxy$, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or $(C_1-C_4)alkyl$ radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$ or (C_1-C_4)alkyl radical;

D is $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 3;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-3.

14. The compound of claim 13 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N; A is S or O;

R^1 is a bromo, chloro, fluoro, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl, (C_1-C_2)alkoxy, $-(NR^{10})_k((C_1-C_2)alkyl)_k-$ cyclopropyl, $-NH_2$ or $-NH((C_1-C_2)alkyl)$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl or (C_1-C_2)alkoxy radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)alkyl)OH$, $(C_1-C_4)alkoxy-(C_1-C_4)alkyl-$, $-((C_1-C_4)alkyl)N(R^5)_2$, $-(CH_2)((C_5-C_6)cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_5-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_2)alkoxy$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_m(C_1-C_2)alkoxy$, $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)(C_1-C_2)alkoxy$, $-(CH_2)((C_5-C_6)cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_5-C_6)cycloalkyl)(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$, $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$, $-D'((C_3-C_6)cycloalkyl)$, $-D'(Q)$, $-D(aryloxy)$, $-D(aryl)$, $-D(heteroaryl)$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k$-D-Q radical, provided R^3 is not $-SO_2NH_2$;

X is a $-N((C_1-C_4)alkyl)_2$ or 4-membered to 10-membered heterocyclyl or heteroaryl ring, having a nitrogen atom ring member bonded directly to the carbon atom adjoining X, optionally substituted with 1-2 radicals of R^8;

wherein each R^{10} is independently a hydrogen or (C_1-C_2)alkyl radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH,

halo, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$, or (C_1-C_2)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or (C_1-C_2)alkyl radical;

D is $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 2;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(O)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_2)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-2.

15. The compound of claim 11 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is $C(R^6)$; A is S, $S(O)_2$ or O;

R^6 is a hydrogen, -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, (C_1-C_4)alkyl or (C_3-C_6)cycloalkyl radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_6)cycloalkyl, $-Z((C_1-C_8)alkoxy)$, $-Z((C_3-C_6)cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(N(R^5)_2)$ or -Z(Q) radical;

R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(N(R^5)_2)$, $-Z(NR^{10}CON(R^5)_2)$, $-Z(NR^{10}(CO)R^5)$, $-Z(NR^{10}CO_2R^5)$, $-Z(S(0)_pR^5)$ or -Z(Q) radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_3-C_8)alkyl, $-((C_1-C_8)alkyl)OH$, $(C_1-C_8)alkoxy-(C_1-C_8)alkyl-$, $-((C_1-C_8)alkyl)N(R^5)_2$, $-((C_1-C_8)alkyl)S(0)_p((C_1-C_8)alkyl)$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(0)_pR^5$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(COR^5)$, $-((C_1-C_8)alkyl)(CO_2R^5)$, $-((C_1-C_8)alkyl)(COR^5)$, $-D'(S(O)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl), $-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^{10}SO_2R^5)$, $-D'(CON(R^5)_2)$, $-D'(NR^{10}CON(R^5)_2)$, $-D'(NR^{10}(CO)R^5)$, $-D'(NR^{10}CO_2R^5)$, -D'(Q),

-D(aryloxy), -D(aryl), -D(heteroaryl), -D((C$_3$-C$_{10}$)cycloalkyl), -D(NR^{10}SO$_2$R^5), -D(CON(R^5)$_2$), -D(S(O)$_q$R^5), -D(NR^{10}CON(R^5)$_2$), -D(NR^{10}(CO)R^5), -D(NR^{10}CO$_2$R^5) or -(NR^{10})$_k$-D-Q radical, provided R^3 is not -SO$_2$NH$_2$;

X is a -(NR^{10})((C$_1$-C$_8$)alkyl)(C$_1$-C$_8$)alkoxy, -(NR^{10})((C$_1$-C$_8$)alkyl)aryloxy, -(NR^{10})S(0)$_p$R^5, -(NR^{10})((C$_1$-C$_8$)alkyl)S(0)$_p$R^5, -(NR^{10})D(C$_1$-C$_8$)alkoxy, -(NR^{10})(CH$_2$)$_m$((C$_3$-C$_{10}$)cycloalkyl)$_k$(CH$_2$)(C$_1$-C$_8$)alkoxy, -(NR^{10})(CH$_2$)((C$_3$-C$_{10}$)cycloalkyl)$_k$(CH$_2$)$_m$(C$_1$-C$_8$)alkoxy, -(NR^{10})(CH$_2$)$_m$((C$_3$-C$_{10}$)cycloalkyl)(CH$_2$)$_m$(C$_1$-C$_8$)alkoxy, -(NR^{10})(CH$_2$)$_m$((C$_3$-C$_{10}$)cycloalkyl)$_k$(CH$_2$)aryloxy, -(NR^{10})(CH$_2$)((C$_3$-C$_{10}$)cycloalkyl)$_k$(CH$_2$)$_m$aryloxy, -(NR^{10})(CH$_2$)$_m$((C$_3$-C$_{10}$)cycloalkyl)(CH$_2$)$_m$aryloxy, -(NR^{10})D(S(0)$_q$R^5), -(NR^{10})D'(S(0)$_q$R^5), -(NR^{10})D(aryl), -(NR^{10})D'(aryl), -(NR^{10})D(heteroaryl), -(NR^{10})D'(heteroaryl), -(NR^{10})D((C$_3$-C$_{10}$)cycloalkyl), -(NR^{10})D'((C$_3$-C$_{10}$)cycloalkyl), -(NR^{10})D(NR^{10}SO$_2$R^5), -(NR^{10})D'(NR^{10}SO$_2$R^5), -(NR^{10})D(CON(R^5)$_2$), -(NR^{10})D'(CON(R^5)$_2$), -(NR^{10})D(CO$_2$R^5), -(NR^{10})D'(CO$_2$R^5), -(NR^{10})D(N(R^5)$_2$), -N(R^5)$_2$, -(NR^{10})D'(N(R^5)$_2$), -(NR^{10})D(NR^{10}CON(R^5)$_2$), -(NR^{10})D'(NR^{10}CON(R^5)$_2$), -(NR^{10})D(NR^{10}(CO)R^5), -(NR^{10})D'(NR^{10}(CO)R^5), -(NR^{10})D(NR^{10}CO$_2$R^5), -(NR^{10})D'(NR^{10}CO$_2$R^5), -(NR^{10})D(COR^5), -(NR^{10})D'(COR^5), -(NR^{10})D-Q, -(NR^{10})D'-Q or Q radical;

wherein each R^{10} is independently a hydrogen or (C$_1$-C$_4$)alkyl radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, -CF$_3$, -OCF$_3$, (C$_1$-C$_4$)alkoxy, -NH$_2$, -NH((C$_1$-C$_4$)alkyl), -N((C$_1$-C$_4$)alkyl)$_2$, or (C$_1$-C$_4$)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, (C_1-C_4)alkyl or (C_3-C_6)cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 4;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^1, R^2, R^3, R^5 and R^6 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$acyloxy, $-(C_3-C_6)$cycloalkyl, $-S-((C_1-C_4)alkyl)_k$-aryl, $-((C_1-C_4)alkyl)_k-SO_2NH$-aryl, aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$, $-S(O)_2(C_1-C_4)$alkyl or Q, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with 1-2 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_4)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 0-3.

16. The compound of claim 15 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is $C(R^6)$; A is S or O;

R^6 is a hydrogen, -OH, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or (C_1-C_4)alkyl radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, $-(NR^{10})_k((C_1-C_2)alkyl)_k$-cyclopropyl or $-(NR^{10})_k((C_1-C_2)alkyl)_k-N(R^{10})_2$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, $-(NR^{10})_k((C_1-C_2)alkyl)_k$-$(C_1-C_4)$alkoxy), $-(NR^{10})_k((C_1-C_2)alkyl)_k-(CON(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(N(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k$-$(S(O)_pR^5)$ or $-(NR^{10})_k((C_1-C_2)alkyl)_k$-Q radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)alkyl)OH$, $(C_1-C_4)alkoxy-(C_1-C_4)alkyl-$, $-((C_1-C_4)alkyl)N(R^5)_2$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl), $-D'((C_3-C_{10})cycloalkyl)$, -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$,

$-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-$ Q radical, provided R^3 is not $-SO_2NH_2$;

X is a $-(N((C_1-C_4)alkyl))-((C_1-C_4)alkyl)aryloxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$, $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)aryloxy$, $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_maryloxy$, $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_maryloxy$, $-(N((C_1-C_4)alkyl))-D(aryl)$, $-(N((C_1-C_4)alkyl))-D'(aryl)$, $-(N((C_1-C_4)alkyl))-D(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D'(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}SO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(N(R^5)_2)$, $-N(R^5)_2$, $-(N((C_1-C_4)alkyl))-D(NR^{10}CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}(CO)R^5)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(COR^5)$, $-(N((C_1-C_4)alkyl))-D-Q$, $-(N((C_1-C_4)alkyl))-D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or $(C_1-C_4)alkyl$ radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, $(C_1-C_4)alkoxy$, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or $(C_1-C_4)alkyl$ radical;

each R^5 is independently a hydrogen, -OH, $(C_1-C_4)alkoxy$, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$ or $(C_1-C_4)alkyl$ radical;

D is $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 3;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-3.

17. The compound of claim 16 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is $C(R^6)$; A is S or O;

R^6 is a hydrogen, -OH, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy or (C_1-C_2)alkyl radical;

R^1 is a bromo, chloro, fluoro, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl, (C_1-C_2)alkoxy, $-(NR^{10})_k((C_1-C_2)alkyl)_k-$cyclopropyl, $-NH_2$ or $-NH((C_1-C_2)alkyl)$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl or (C_1-C_2)alkoxy radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)\text{alkyl})OH$, $(C_1-C_4)\text{alkoxy}-(C_1-C_4)\text{alkyl}-$, $-((C_1-C_4)\text{alkyl})N(R^5)_2$, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)OH$, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_m(C_1-C_2)\text{alkoxy}$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(C_1-C_2)\text{alkoxy}$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)(C_1-C_2)\text{alkoxy}$, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl), $-D'((C_3-C_6)\text{cycloalkyl})$, -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k$-D-Q radical, provided R^3 is not $-SO_2NH_2$;

X is a $-N((C_1-C_4)\text{alkyl})_2$ or 4-membered to 10-membered heterocyclyl or heteroaryl ring, having a nitrogen atom ring member bonded directly to the carbon atom adjoining X, optionally substituted with 1-2 radicals of R^8;

wherein each R^{10} is independently a hydrogen or (C_1-C_2)alkyl radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH,

halo, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$, or (C_1-C_2)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or (C_1-C_2)alkyl radical;

D is $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 2;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_2)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-2.

18. The compound of claim 10 which is:

2-Methyl-6-phenyl-4-piperidylthiopheno[3,2-d] pyrimidine;

6-(4-Chlorophenyl)-2-methyl-4-piperidylthiopheno[3,2-d] pyrimidine;

6-(*tert*-Butyl)-2-methyl-4-piperidylthiopheno[3,2-d] pyrimidine;

6-(4-Chlorophenyl)-2-methyl-4-piperidinylfurano-[3,2-d] pyrimidine;

6-(4-Chlorophenyl)-2-ethyl-4-piperidinylfurano[3,2-d] pyrimidine;

6-(*tert*-Butyl)-2-methyl-4-piperidylthiopheno[3,2-*d*] pyrimidin-1-ol;

2-Methyl-6-phenyl-4-piperidylthiopheno[3,2-*d*]pyrimidin-1-ol;

6-(4-Chloro-phenyl)-2-methyl-4-piperidylthiopheno[3,2-*d*]pyrimidin-1-ol;

6-Phenyl-4-piperidyl-2-(trifluoromethyl)thiophene[3,2-*d*]pyrimidine;

2-Methyl-6-phenyl-4-(3-pyrrolinyl)furano[3,2-*d*] pyrimidine;

6-(4-Fluorophenyl)-2-methyl-4-piperidylthiopheno[3,2-*d*] pyrimidine;

2-Methyl-6-phenyl-4-(2-1,2,3,4-tetrahydroisoquinolyl) thiopheno[3,2-*d*]pyrimidine;

2-Methyl-6-phenyl-4-(1,2,5,6-tetrahydropyridyl) thiopheno[3,2-*d*]pyrimidine;

2-Methyl-6-phenyl-4-piperidylfurano[3,2-*d*]pyrimidine;

5-Methyl-2-phenyl-7-piperidylfurano[3,2-b]pyridine;

2-Butyl-5-methyl-7-piperidylfurano[3,2-b]pyridine;

2-(4-Fluorophenyl)-5-methyl-7-piperidylfurano[3,2-b] pyridine; or

5-Methyl-7-piperidyl-2-(4-piperidylphenyl)furano[3,2-b] pyridine; or

a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a compound of claims 1 to 18 and a pharmaceutically acceptable carrier.

20. Use of a compound of claims 1 to 18 for the preparation of a composition for use in modulating feeding behavior.

21. Use of a compound of claims 1 to 18 for the preparation of a composition for use in the prophylaxis or treatment of obesity.

22. Use of a compound of claims 1 to 18 for the preparation of a composition for use in the prophylaxis or treatment of diabetes.

23. Use of a compound of claims 1 to 18 for the preparation of a composition for use in the prophylaxis or treatment of a tumor disease.

24. Use of a compound of claims 1 to 18 for the preparation of a composition for use in the prophylaxis or treatment of an inflammatory disease or disorder.

25. Use of a compound of claims 1 to 18 for the preparation of a composition for use in the prophylaxis or treatment of a diseases or disorder which can be effected or facilitated by modulating CRF in a warm blooded animal.

26. Use of a compound of claims 1 to 18 for the preparation of a composition for use in treating rheumatoid arthritis; osteoarthritis; pain; asthma; psoriasis; allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders; stress-induced psychotic episodes; pain perception; fibromyalgia; mood disorders; depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; fever; human immunodeficiency virus (HIV) infections; neurodegenerative diseases; Alzheimer's disease;

Parkinson's disease; Huntington's disease; gastrointestinal diseases; eating disorders; anorexia; bulimia nervosa; hemorrhagic stress; chemical dependencies; addictions; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia; diarrhea; or colonic hypersensitivity.

27. A method for modulating feeding behavior which comprises administering to a warm blood animal an effective amount of a compound of claims 1 to 18.

28. A method for the prophylaxis or treatment of obesity which comprises administering to a warm blood animal an effective amount of a compound of claims 1 to 18.

29. A method for the prophylaxis or treatment of diabetes which comprises administering to a warm blood animal an effective amount of a compound of claims 1 to 18.

30. A method for the prophylaxis or treatment of a tumor disease in a warm blooded animal comprising administering to the warm blooded animal an effective amount of a compound of claims 1 to 18.

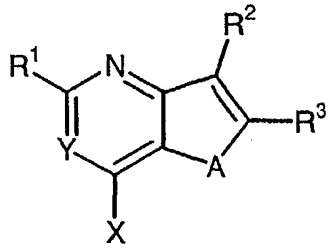
31. A method for the prophylaxis or treatment of an inflammatory disease or disorder comprising administering to the warm blood animal an effective amount of a compound of claims 1 to 18.

32. A method for the prophylaxis or treatment of a diseases or disorder which can be effected or facilitated by modulating CRF in a warm blooded animal comprising administering to the warm blood animal an effective amount of a compound of claims 1 to 18.

33. The method of Claim 32 wherein the disease or disorder is rheumatoid arthritis; osteoarthritis; pain; asthma; psoriasis; allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders; stress-induced psychotic episodes; pain perception; fibromyalgia; mood disorders; depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; fever; human immunodeficiency virus (HIV) infections; neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; Huntington's disease; gastrointestinal diseases; eating disorders; anorexia; bulimia nervosa; hemorrhagic stress; chemical dependencies; addictions; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension;

tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia; diarrhea; or colonic hypersensitivity.

34. A method for modulating feeding behavior, obesity or diabetes, or another disease state associated with the same or related pathway which modulates feeding behavior, obesity or diabetes which comprises administering to a warm blood animal an effective amount of a compound of formula



or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N or $C(R^6)$; A is O, S, $S(O)$, $S(O)_2$, N-H, $N-R^4$ or CR^4R^7;

R^6 is a hydrogen, -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, $-Z$(aryl), $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl or -Z(Q) radical;

R^1 and X are each independently a hydrogen, halo, -OH, $-NO_2$, -NHOH, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(0)_pR^5)$ or -Z(Q) radical; or

X and A, when A is N or C, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or

bicyclic carbocyclic or heterocyclic ring which is optionally substituted with 1-2 radicals of R^8;

R^2 and R^3 are each independently a hydrogen, halo, -OH, $-NO_2$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$; provided R^2 is not an optionally substituted aryl or heteroaryl radical;

R^4 is a hydrogen, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$ radical;

each R^5 and R^7 are each independently a hydrogen, -OH, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl or (C_3-C_{10})cycloalkyl radical;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, or (C_1-C_8)alkyl radical;

Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$; and D' is $-((C_1-C_8)alkyl)_k-$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 6;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 is optionally substituted with one or more radicals of halo, $-CF_3$, $-OCF_3$, -Z(COOH), -Z(OH), $-Z(NO_2)$, -Z(SH), $-(C_1-C_8)$alkyl, $-(C_1-C_8)$acyloxy, $-(C_3-C_{10})$cycloalkyl, $-S-((C_1-C_8)alkyl)_k$-aryl, $-((C_1-C_8)alkyl)_k-SO_2NH$-aryl, $-S-(C_1-C_8)$alkyl, $-Z((C_1-C_8)$alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})$cycloalkyl), $-Z(NR^9SO_2R^9)$, $-Z(CON(R^9)_2)$, $-Z(CO_2R^9)$, $-Z(N(R^9)_2)$, $-Z(NR^9CON(R^9)_2)$, $-Z(NR^9(CO)R^9)$, $-Z(NR^9CO_2R^9)$, $-Z(COR^9)$, $-Z(S(0)_pR^9)$ or -Z(Q), wherein each R^9 is independently a hydrogen or (C_1-C_8)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with one or more radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_8)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 0-4.

35. The method of claim 34, wherein Y is N or $C(R^6)$; A is O, S, S(O), $S(O)_2$, N-H, $N-R^4$ or CR^4R^7;

R^6 is a hydrogen, -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)$alkyl), $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl or -Z(Q) radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)$alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})$cycloalkyl), $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or -Z(Q) radical;

R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)$alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})$cycloalkyl), $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or -Z(Q) radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_1-C_8)alkyl, $-((C_1-C_8)$alkyl)OH, (C_1-C_8)alkoxy-(C_1-C_8)alkyl-, $-((C_1-C_8)$alkyl)$N(R^5)_2$, $-((C_1-C_8)$alkyl)$S(O)_p((C_1-C_8)$alkyl), $-(CH_2)((C_3-C_{10})$cycloalkyl$)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)_k(CH_2)$OH, $-(CH_2)((C_3-C_{10})$cycloalkyl$)_k(CH_2)_m(C_1-C_8)$alkoxy, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_m(C_1-C_8)$alkoxy, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)_k(CH_2)(C_1-C_8)$alkoxy, $-(CH_2)((C_3-C_{10})$cycloalkyl$)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_mS(O)_pR^5$, $-D'(S(O)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl), $-D'((C_3-C_{10})$cycloalkyl), $-D'(NR^5SO_2R^5)$, $-D'(CON(R^5)_2)$, $-D'(CO_2R^5)$, $-D'(NR^5CON(R^5)_2)$, $-D'(NR^5(CO)R^5)$, $-D'(NR^5CO_2R^5)$, $-D'(COR^5)$, -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), $-D((C_3-C_{10})$cycloalkyl), $-D(NR^5SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(CO_2R^5)$, $-D(S(O)_qR^5)$, $-D(NR^5CON(R^5)_2)$,

$-D(NR^5(CO)R^5)$, $-D(NR^5CO_2R^5)$, $-D(COR^5)$ or $-(NR^5)_k-D-Q$ radical;

R^4 is a (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(0)_pR^5)$ or $-Z(Q)$ radical;

X is a (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-(NR^5)_k((C_1-C_8)alkyl)(C_1-C_8)alkoxy$, $-(NR^5)_k((C_1-C_8)alkyl)aryloxy$, $-(NR^5)((C_1-C_8)alkyl)_kS(0)_pR^5$, $-(NR^5)_k((C_1-C_8)alkyl)S(0)_pR^5$, $-(NR^5)D(C_1-C_8)alkoxy$, $-(NR^5)(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$, $-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$, $-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$, $-(NR^5)(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)aryloxy$, $-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$, $-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_maryloxy$, $-Z(S(0)_qR^5)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$ or $-Z(Q)$ radical; or

X and A, when A is N or C, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic carbocyclic or heterocyclic ring which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, or (C_1-C_8)alkyl radical;

each R^5 and R^7 are each independently a hydrogen, -OH, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl or (C_3-C_{10})cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 6;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 is optionally substituted with one or more radicals of halo, $-CF_3$, $-OCF_3$, -Z(COOH), -Z(OH), $-Z(NO_2)$, -Z(SH), $-(C_1-C_8)$alkyl, $-(C_1-C_8)$acyloxy, $-(C_3-C_{10})$cycloalkyl, $-S-((C_1-C_8)alkyl)_k$-aryl, $-((C_1-C_8)alkyl)_k-SO_2NH$-aryl, $-S-(C_1-C_8)$alkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^9SO_2R^9)$, $-Z(CON(R^9)_2)$, $-Z(CO_2R^9)$, $-Z(N(R^9)_2)$, $-Z(NR^9CON(R^9)_2)$, $-Z(NR^9(CO)R^9)$, $-Z(NR^9CO_2R^9)$, $-Z(COR^9)$, $-Z(S(O)_pR^9)$ or -Z(Q), wherein each R^9 is independently a hydrogen or (C_1-C_8)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with one or more radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_8)alkyl;

or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

36. The method of claim 35, wherein Y is N or $C(R^6)$; A is O, S, S(O), $S(O)_2$, N-H, $N-R^4$ or CR^4R^7;

R^6 is a hydrogen, -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl or -Z(Q) radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or -Z(Q) radical;

R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(S(O)_pR^5)$ or -Z(Q) radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_3-C_8)alkyl, $-((C_1-C_8)alkyl)OH$, $(C_1-C_8)alkoxy-(C_1-C_8)alkyl-$, $-((C_1-C_8)alkyl)N(R^5)_2$, $-((C_1-C_8)alkyl)S(O)_p((C_1-C_8)alkyl)$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$,

$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(O)_pR^5$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(CO_2R^5)$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(COR^5)$,
$-((C_1-C_8)alkyl)(CO_2R^5)$, $-((C_1-C_8)alkyl)(COR^5)$,
$-D'(S(O)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl),
$-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^5SO_2R^5)$, $-D'(CON(R^5)_2)$,
$-D'(NR^5CON(R^5)_2)$, $-D'(NR^5(CO)R^5)$, $-D'(NR^5CO_2R^5)$, -D'(Q),
-D(aryloxy), -D(aryl), -D(heteroaryl),
$-D((C_3-C_{10})cycloalkyl)$, $-D(NR^5SO_2R^5)$, $-D(CON(R^5)_2)$,
$-D(S(O)_qR^5)$, $-D(NR^5CON(R^5)_2)$, $-D(NR^5(CO)R^5)$, $-D(NR^5CO_2R^5)$ or
$-(NR^5)_k$-D—Q radical;

R^4 is a (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl,
$-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl),
-Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$,
$-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$,
$-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or -Z(Q)
radical;

X is a $-(NR^5)_k((C_1-C_8)alkyl)(C_1-C_8)alkoxy$,
$-(NR^5)_k((C_1-C_8)alkyl)aryloxy$, $-(NR^5)((C_1-C_8)alkyl)_kS(O)_pR^5$,
$-(NR^5)_k((C_1-C_8)alkyl)S(O)_pR^5$, $-(NR^5)D(C_1-C_8)alkoxy$,
$-(NR^5)(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$,
$-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^5)(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)aryloxy$,
$-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$,
$-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_maryloxy$, $-Z(S(O)_qR^5)$,
-Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$,
$-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$,
$-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$ or
-Z(Q) radical; or

X and A, when A is N or C, together with the adjoining
carbon atoms form a 5-membered to 10-membered mono- or

bicyclic carbocyclic or heterocyclic ring which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, or (C_1-C_8)alkyl radical;

each R^5 and R^7 are each independently a hydrogen, -OH, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl or (C_3-C_{10})cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 6;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-Z(COOH)$, $-Z(OH)$, $-Z(NO_2)$, $-Z(SH)$, $-(C_1-C_8)$alkyl, $-(C_1-C_8)$acyloxy, $-(C_3-C_{10})$cycloalkyl, $-S-((C_1-C_8)alkyl)_k$-aryl, $-((C_1-C_8)alkyl)_k-SO_2NH$-aryl, $-S-(C_1-C_8)$alkyl, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^9SO_2R^9)$, $-Z(CON(R^9)_2)$, $-Z(CO_2R^9)$, $-Z(N(R^9)_2)$, $-Z(NR^9CON(R^9)_2)$, $-Z(NR^9(CO)R^9)$, $-Z(NR^9CO_2R^9)$, $-Z(COR^9)$, $-Z(S(0)_pR^9)$ or $-Z(Q)$, wherein each R^9 is independently a hydrogen or

(C_1-C_8)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with 1-3 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_8)alkyl;

or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

37. The method of claim 36, wherein Y is N; A is O, S, $S(O)_2$, N-H, $N-R^4$ or CHR^4;

R^1 is a hydrogen, halo, $-OH$, $-NO_2$, $-NHOH$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_6)cycloalkyl, $-Z((C_1-C_8)$alkoxy), $-Z((C_3-C_6)$cycloalkyl), $-Z(NR^{10}SO_2R^5)$, $-Z(N(R^5)_2)$ or $-Z(Q)$ radical;

R^2 is a hydrogen, halo, $-OH$, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)$alkoxy), $-Z$(aryloxy), $-Z$(aryl), $-Z$(heteroaryl), $-Z((C_3-C_{10})$cycloalkyl), $-Z(NR^{10}SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(N(R^5)_2)$, $-Z(NR^{10}CON(R^5)_2)$, $-Z(NR^{10}(CO)R^5)$, $-Z(NR^{10}CO_2R^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$ radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_3-C_8)alkyl, $-((C_1-C_8)$alkyl)OH, (C_1-C_8)alkoxy-(C_1-C_8)alkyl-, $-((C_1-C_8)$alkyl)$N(R^5)_2$, $-((C_1-C_8)$alkyl)$S(O)_p((C_1-C_8)$alkyl), $-(CH_2)((C_3-C_{10})$cycloalkyl$)_k(CH_2)_m$OH, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_m$OH, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)_k(CH_2)$OH, $-(CH_2)((C_3-C_{10})$cycloalkyl$)_k(CH_2)_m(C_1-C_8)$alkoxy, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_m(C_1-C_8)$alkoxy, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)_k(CH_2)(C_1-C_8)$alkoxy, $-(CH_2)((C_3-C_{10})$cycloalkyl$)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_mN(R^5)_2$,

$-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(O)_pR^5$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(CO_2R^5)$,
$-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(COR^5)$,
$-((C_1-C_8)alkyl)(CO_2R^5)$, $-((C_1-C_8)alkyl)(COR^5)$,
$-D'(S(O)_qR^5)$, $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$,
$-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^{10}SO_2R^5)$, $-D'(CON(R^5)_2)$,
$-D'(NR^{10}CON(R^5)_2)$, $-D'(NR^{10}(CO)R^5)$, $-D'(NR^{10}CO_2R^5)$, $-D'(Q)$,
$-D(aryloxy)$, $-D(aryl)$, $-D(heteroaryl)$,
$-D((C_3-C_{10})cycloalkyl)$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$,
$-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$
or $-(NR^{10})_k-D-Q$ radical;

R^4 is a (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, $-N(R^5)_2$ or $-Z(Q)$ radical;

X is a $-(NR^{10})((C_1-C_8)alkyl)(C_1-C_8)alkoxy$,
$-(NR^{10})((C_1-C_8)alkyl)aryloxy$, $-(NR^{10})S(O)_pR^5$,
$-(NR^{10})((C_1-C_8)alkyl)S(O)_pR^5$, $-(NR^{10})D(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)aryloxy$,
$-(NR^{10})(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_maryloxy$,
$-(NR^{10})D(S(O)_qR^5)$, $-(NR^{10})D'(S(O)_qR^5)$, $-(NR^{10})D(aryl)$,
$-(NR^{10})D'(aryl)$, $-(NR^{10})D(heteroaryl)$,
$-(NR^{10})D'(heteroaryl)$, $-(NR^{10})D((C_3-C_{10})cycloalkyl)$,
$-(NR^{10})D'((C_3-C_{10})cycloalkyl)$, $-(NR^{10})D(NR^{10}SO_2R^5)$,
$-(NR^{10})D'(NR^{10}SO_2R^5)$, $-(NR^{10})D(CON(R^5)_2)$, $-(NR^{10})D'(CON(R^5)_2)$,
$-(NR^{10})D(CO_2R^5)$, $-(NR^{10})D'(CO_2R^5)$, $-(NR^{10})D(N(R^5)_2)$, $-N(R^5)_2$,
$-(NR^{10})D'(N(R^5)_2)$, $-(NR^{10})D(NR^{10}CON(R^5)_2)$,
$-(NR^{10})D'(NR^{10}CON(R^5)_2)$, $-(NR^{10})D(NR^{10}(CO)R^5)$,
$-(NR^{10})D'(NR^{10}(CO)R^5)$, $-(NR^{10})D(NR^{10}CO_2R^5)$,
$-(NR^{10})D'(NR^{10}CO_2R^5)$, $-(NR^{10})D(COR^5)$, $-(NR^{10})D'(COR^5)$,
$-(NR^{10})D-Q$, $-(NR^{10})D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or (C_1-C_4)alkyl radical; or

X and A, when A is N or C, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic heterocyclic ring which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or (C_1-C_4)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, (C_1-C_4)alkyl or (C_3-C_6)cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 4;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^1, R^2, R^3, R^4 and R^5 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$acyloxy, $-(C_3-C_6)$cycloalkyl, $-S-((C_1-C_4)alkyl)_k$-aryl, $-((C_1-C_4)alkyl)_k-SO_2NH$-aryl, aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$,

$-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$, $-S(0)_2(C_1-C_4)$alkyl or Q, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with 1-2 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_4)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 0-3;

or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

38. The method of claim 37, wherein Y is N; A is O, S, N-H or $N-R^4$;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, $-(NR^{10})_k((C_1-C_2)alkyl)_k-$cyclopropyl or $-(NR^{10})_k((C_1-C_2)alkyl)_k-N(R^{10})_2$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(C_1-C_4)alkoxy)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(CON(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(N(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(S(0)_pR^5)$ or $-(NR^{10})_k((C_1-C_2)alkyl)_k-Q$ radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)alkyl)OH$, $(C_1-C_4)alkoxy-(C_1-C_4)alkyl-$, $-((C_1-C_4)alkyl)N(R^5)_2$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$,

$-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$,
$-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_mN(R^5)_2$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mN(R^5)_2$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)N(R^5)_2$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mS(O)_pR^5$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(CO_2R^5)$,
$-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(COR^5)$, -D'($S(O)_qR^5$), -D'(aryloxy), -D'(aryl), -D'(heteroaryl), -D'((C_3-C_{10})cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), -D($NR^{10}SO_2R^5$), -D($CON(R^5)_2$), -D($S(O)_qR^5$), -D($NR^{10}CON(R^5)_2$), -D($NR^{10}(CO)R^5$), -D($NR^{10}CO_2R^5$) or $-(NR^{10})_k$-D-Q radical;

R^4 is a (C_1-C_4)alkyl radical;

X is a $-(N((C_1-C_4)alkyl))-((C_1-C_4)alkyl)aryloxy$,
$-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$,
$-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$,
$-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$,
$-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)aryloxy$,
$-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_maryloxy$,
$-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_maryloxy$,
$-(N((C_1-C_4)alkyl))$-D(aryl), $-(N((C_1-C_4)alkyl))$-D'(aryl), $-(N((C_1-C_4)alkyl))$-D(heteroaryl), $-(N((C_1-C_4)alkyl))$-D'(heteroaryl), $-(N((C_1-C_4)alkyl))-D(NR^{10}SO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(N(R^5)_2)$, $-N(R^5)_2$, $-(N((C_1-C_4)alkyl))-D(NR^{10}CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}(CO)R^5)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(COR^5)$, $-(N((C_1-C_4)alkyl))$-D-Q, $-(N((C_1-C_4)alkyl))$-D'-Q or Q radical;

wherein each R^{10} is independently a hydrogen or (C_1-C_4)alkyl radical; or

X and A, when A is N, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic heterocyclyl moiety which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or (C_1-C_4)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$ or (C_1-C_4)alkyl radical;

D is $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 3;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-3;

or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

39. The method of claim 38, wherein Y is N; A is O, S or N-H;

R^1 is a bromo, chloro, fluoro, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl, (C_1-C_2)alkoxy, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k$-cyclopropyl, $-NH_2$ or $-NH((C_1-C_2)\text{alkyl})$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl or (C_1-C_2)alkoxy radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)\text{alkyl})OH$, (C_1-C_4)alkoxy-(C_1-C_4)alkyl-, $-((C_1-C_4)\text{alkyl})N(R^5)_2$, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)OH$, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_m(C_1-C_2)$alkoxy, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(C_1-C_2)$alkoxy, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)(C_1-C_2)$alkoxy, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl), $-D'((C_3-C_6)\text{cycloalkyl})$, -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$,

$-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-$ Q radical;

X is a $-N((C_1-C_4)alkyl)_2$ or 4-membered to 10-membered heterocyclyl or heteroaryl ring, having a nitrogen atom ring member bonded directly to the carbon atom adjoining X, optionally substituted with 1-2 radicals of R^8;

wherein each R^{10} is independently a hydrogen or (C_1-C_2)alkyl radical; or

X and A, when A is N, together with the adjoining carbon atoms form a 8-membered to 10-membered bicyclic heterocyclyl moiety which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$, or (C_1-C_2)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or (C_1-C_2)alkyl radical;

D is $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 2;
each p is independently an integer between 0 and 2; and

each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_2)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-2;

or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

40. The method of claim 36, wherein Y is $C(R^6)$; A is O, S, $S(O)_2$, N-H, $N-R^4$ or CHR^4;

R^6 is a hydrogen, -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, (C_1-C_4)alkyl or (C_3-C_6)cycloalkyl radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_6)cycloalkyl, $-Z((C_1-C_8)alkoxy)$, $-Z((C_3-C_6)cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(N(R^5)_2)$ or -Z(Q) radical;

R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(N(R^5)_2)$, $-Z(NR^{10}CON(R^5)_2)$, $-Z(NR^{10}(CO)R^5)$, $-Z(NR^{10}CO_2R^5)$,

$-Z(S(O)_pR^5)$ or $-Z(Q)$ radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_3-C_8)alkyl, $-((C_1-C_8)alkyl)OH$, $(C_1-C_8)alkoxy-(C_1-C_8)alkyl-$, $-((C_1-C_8)alkyl)N(R^5)_2$, $-((C_1-C_8)alkyl)S(O)_p((C_1-C_8)alkyl)$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(COR^5)$, $-((C_1-C_8)alkyl)(CO_2R^5)$, $-((C_1-C_8)alkyl)(COR^5)$, $-D'(S(O)_qR^5)$, $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$, $-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^{10}SO_2R^5)$, $-D'(CON(R^5)_2)$, $-D'(NR^{10}CON(R^5)_2)$, $-D'(NR^{10}(CO)R^5)$, $-D'(NR^{10}CO_2R^5)$, $-D'(Q)$, $-D(aryloxy)$, $-D(aryl)$, $-D(heteroaryl)$, $-D((C_3-C_{10})cycloalkyl)$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-Q$ radical;

R^4 is a (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, $-N(R^5)_2$ or $-Z(Q)$ radical;

X is a $-(NR^{10})((C_1-C_8)alkyl)(C_1-C_8)alkoxy$, $-(NR^{10})((C_1-C_8)alkyl)aryloxy$, $-(NR^{10})S(O)_pR^5$, $-(NR^{10})((C_1-C_8)alkyl)S(O)_pR^5$, $-(NR^{10})D(C_1-C_8)alkoxy$, $-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$, $-(NR^{10})(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$, $-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$,

$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)aryloxy$,
$-(NR^{10})(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$,
$-(NR^{10})(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_maryloxy$,
$-(NR^{10})D(S(0)_qR^5)$, $-(NR^{10})D'(S(0)_qR^5)$, $-(NR^{10})D(aryl)$,
$-(NR^{10})D'(aryl)$, $-(NR^{10})D(heteroaryl)$,
$-(NR^{10})D'(heteroaryl)$, $-(NR^{10})D((C_3-C_{10})cycloalkyl)$,
$-(NR^{10})D'((C_3-C_{10})cycloalkyl)$, $-(NR^{10})D(NR^{10}SO_2R^5)$,
$-(NR^{10})D'(NR^{10}SO_2R^5)$, $-(NR^{10})D(CON(R^5)_2)$, $-(NR^{10})D'(CON(R^5)_2)$,
$-(NR^{10})D(CO_2R^5)$, $-(NR^{10})D'(CO_2R^5)$, $-(NR^{10})D(N(R^5)_2)$, $-N(R^5)_2$,
$-(NR^{10})D'(N(R^5)_2)$, $-(NR^{10})D(NR^{10}CON(R^5)_2)$,
$-(NR^{10})D'(NR^{10}CON(R^5)_2)$, $-(NR^{10})D(NR^{10}(CO)R^5)$,
$-(NR^{10})D'(NR^{10}(CO)R^5)$, $-(NR^{10})D(NR^{10}CO_2R^5)$,
$-(NR^{10})D'(NR^{10}CO_2R^5)$, $-(NR^{10})D(COR^5)$, $-(NR^{10})D'(COR^5)$,
$-(NR^{10})D-Q$, $-(NR^{10})D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or (C_1-C_4)alkyl radical; or

X and A, when A is N or C, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic heterocyclic ring which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or (C_1-C_4)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, (C_1-C_4)alkyl or (C_3-C_6)cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 4;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^1, R^2, R^3, R^4, R^5 and R^6 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$acyloxy, $-(C_3-C_6)$cycloalkyl, $-S-((C_1-C_4)alkyl)_k$-aryl, $-((C_1-C_4)alkyl)_k-SO_2NH$-aryl, aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$, $-S(0)_2(C_1-C_4)$alkyl or Q, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with 1-2 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_4)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 0-3;

or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

41. The method of claim 40, wherein Y is $C(R^6)$; A is O, S, N-H or $N-R^4$;

R^6 is a hydrogen, -OH, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or (C_1-C_4)alkyl radical;

R^1 is a hydrogen, halo, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, $-(NR^{10})_k((C_1-C_2)alkyl)_k-$cyclopropyl or $-(NR^{10})_k((C_1-C_2)alkyl)_k-N(R^{10})_2$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(C_1-C_4)alkoxy)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(CON(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(N(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(S(O)_pR^5)$ or $-(NR^{10})_k((C_1-C_2)alkyl)_k-Q$ radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)alkyl)OH$, $(C_1-C_4)alkoxy-(C_1-C_4)alkyl-$, $-((C_1-C_4)alkyl)N(R^5)_2$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(COR^5)$, -D'$(S(O)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl), -D'$((C_3-C_{10})$cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-$Q radical;

R^4 is a (C_1-C_4)alkyl radical;

X is a -(N((C$_1$-C$_4$)alkyl))-((C$_1$-C$_4$)alkyl)aryloxy, -(N((C$_1$-C$_4$)alkyl))-(CH$_2$)$_m$((C$_3$-C$_6$)cycloalkyl)$_k$(CH$_2$)(C$_1$-C$_4$)alkoxy, -(N((C$_1$-C$_4$)alkyl))-(CH$_2$)((C$_3$-C$_6$)cycloalkyl)$_k$(CH$_2$)$_m$(C$_1$-C$_4$)alkoxy, -(N((C$_1$-C$_4$)alkyl))-(CH$_2$)$_m$((C$_3$-C$_6$)cycloalkyl)(CH$_2$)$_m$(C$_1$-C$_4$)alkoxy, -(N((C$_1$-C$_4$)alkyl))-(CH$_2$)$_m$((C$_3$-C$_6$)cycloalkyl)$_k$(CH$_2$)aryloxy, -(N((C$_1$-C$_4$)alkyl))-(CH$_2$)((C$_3$-C$_6$)cycloalkyl)$_k$(CH$_2$)$_m$aryloxy, -(N((C$_1$-C$_4$)alkyl))-(CH$_2$)$_m$((C$_3$-C$_6$)cycloalkyl)(CH$_2$)$_m$aryloxy, -(N((C$_1$-C$_4$)alkyl))-D(aryl), -(N((C$_1$-C$_4$)alkyl))-D'(aryl), -(N((C$_1$-C$_4$)alkyl))-D(heteroaryl), -(N((C$_1$-C$_4$)alkyl))-D'(heteroaryl), -(N((C$_1$-C$_4$)alkyl))-D(NR^{10}SO$_2$R^5), -(N((C$_1$-C$_4$)alkyl))-D(CON(R^5)$_2$), -(N((C$_1$-C$_4$)alkyl))-D(CO$_2$R^5), -(N((C$_1$-C$_4$)alkyl))-D(N(R^5)$_2$), -N(R^5)$_2$, -(N((C$_1$-C$_4$)alkyl))-D(NR^{10}CON(R^5)$_2$), -(N((C$_1$-C$_4$)alkyl))-D(NR^{10}(CO)R^5), -(N((C$_1$-C$_4$)alkyl))-D(NR^{10}CO$_2$R^5), -(N((C$_1$-C$_4$)alkyl))-D(COR^5), -(N((C$_1$-C$_4$)alkyl))-D-Q, -(N((C$_1$-C$_4$)alkyl))-D'-Q or Q radical;

wherein each R^{10} is independently a hydrogen or (C$_1$-C$_4$)alkyl radical; or

X and A, when A is N, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic heterocyclyl moiety which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, -CF$_3$, -OCF$_3$, (C$_1$-C$_4$)alkoxy, -NH$_2$, -NH((C$_1$-C$_4$)alkyl), -N((C$_1$-C$_4$)alkyl)$_2$, or (C$_1$-C$_4$)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$ or (C_1-C_4)alkyl radical;

D is $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 3;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2, and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-3;

or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

42. The method of claim 41, wherein Y is $C(R^6)$; A is O, S or N-H;

R^6 is a hydrogen, -OH, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy or (C_1-C_2)alkyl radical;

R^1 is a bromo, chloro, fluoro, -OH, $-NO_2$, -NHOH, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl, (C_1-C_2)alkoxy, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k$-cyclopropyl, $-NH_2$ or $-NH((C_1-C_2)\text{alkyl})$ radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl or (C_1-C_2)alkoxy radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)\text{alkyl})OH$, $(C_1-C_4)\text{alkoxy}-(C_1-C_4)\text{alkyl}-$, $-((C_1-C_4)\text{alkyl})N(R^5)_2$, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)OH$, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_m(C_1-C_2)\text{alkoxy}$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(C_1-C_2)\text{alkoxy}$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)(C_1-C_2)\text{alkoxy}$, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$, $-D'(\text{aryloxy})$, $-D'(\text{aryl})$, $-D'(\text{heteroaryl})$, $-D'((C_3-C_6)\text{cycloalkyl})$, $-D'(Q)$, $-D(\text{aryloxy})$, $-D(\text{aryl})$, $-D(\text{heteroaryl})$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k$-D-Q radical;

X is a $-N((C_1-C_4)\text{alkyl})_2$ or 4-membered to 10-membered heterocyclyl or heteroaryl ring, having a nitrogen atom ring member bonded directly to the carbon atom adjoining X, optionally substituted with 1-2 radicals of R^8;

wherein each R^{10} is independently a hydrogen or (C_1-C_2)alkyl radical; or

X and A, when A is N, together with the adjoining carbon atoms form a 8-membered to 10-membered bicyclic heterocyclyl moiety which is optionally substituted with 1-2 radicals of R^8;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$, or (C_1-C_2)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or (C_1-C_2)alkyl radical;

D is $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

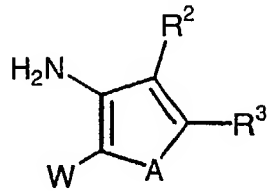
each k is independently 0 or 1;
each m is independently an integer between 0 and 2;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_2)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1, R^2 and R^3 is 1-2;

or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

43. A compound of formula



wherein A is O, S, S(O), S(O)2, N-H, N-R^4 or CR^4R^7; W is -CN or -C(O)L; wherein L is a halo or C1-C2 alkoxy radical;

R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)$alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})$cycloalkyl), $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or -Z(Q) radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_1-C_8)alkyl, $-((C_1-C_8)$alkyl)OH, (C_1-C_8)alkoxy-(C_1-C_8)alkyl-, $-((C_1-C_8)$alkyl)$N(R^5)_2$, $-((C_1-C_8)$alkyl)$S(O)_p((C_1-C_8)$alkyl), $-(CH_2)((C_3-C_{10})$cycloalkyl$)_k(CH_2)_m$OH, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_m$OH, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)_k(CH_2)$OH, $-(CH_2)((C_3-C_{10})$cycloalkyl$)_k(CH_2)_m(C_1-C_8)$alkoxy, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_m(C_1-C_8)$alkoxy, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)_k(CH_2)(C_1-C_8)$alkoxy, $-(CH_2)((C_3-C_{10})$cycloalkyl$)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})$cycloalkyl$)(CH_2)_mN(R^5)_2$,

$-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(O)_pR^5$, $-D'(S(O)_qR^5)$, $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$, $-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^5SO_2R^5)$, $-D'(CON(R^5)_2)$, $-D'(CO_2R^5)$, $-D'(NR^5CON(R^5)_2)$, $-D'(NR^5(CO)R^5)$, $-D'(NR^5CO_2R^5)$, $-D'(COR^5)$, $-D'(Q)$, $-D(aryloxy)$, $-D(aryl)$, $-D(heteroaryl)$, $-D((C_3-C_{10})cycloalkyl)$, $-D(NR^5SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(CO_2R^5)$, $-D(S(O)_qR^5)$, $-D(NR^5CON(R^5)_2)$, $-D(NR^5(CO)R^5)$, $-D(NR^5CO_2R^5)$, $-D(COR^5)$ or $-(NR^5)_k-D-Q$ radical;

R^4 is a $(C_1-C_8)alkyl$, $(C_3-C_{10})cycloalkyl$, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$ radical;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, $(C_1-C_8)alkoxy$, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, or $(C_1-C_8)alkyl$ radical;

each R^5 and R^7 are each independently a hydrogen, -OH, $(C_1-C_8)alkoxy$, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, $(C_1-C_8)alkyl$ or $(C_3-C_{10})cycloalkyl$ radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

each k is independently 0 or 1;

each m is independently an integer between 0 and 6; each p is independently an integer between 0 and 2; and each q is independently 1 or 2; and

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of R^2, R^3, R^4, R^5, R^7 and R^8 is optionally substituted with one or more radicals of halo, $-CF_3$, $-OCF_3$, $-Z(COOH)$, $-Z(OH)$, $-Z(NO_2)$, $-Z(SH)$, $-(C_1-C_8)$alkyl, $-(C_1-C_8)$acyloxy, $-(C_3-C_{10})$cycloalkyl, $-S-((C_1-C_8)alkyl)_k-aryl$, $-((C_1-C_8)alkyl)_k-SO_2NH-aryl$, $-S-(C_1-C_8)$alkyl, $-Z((C_1-C_8)$alkoxy), $-Z$(aryloxy), $-Z$(aryl), $-Z$(heteroaryl), $-Z((C_3-C_{10})$cycloalkyl), $-Z(NR^9SO_2R^9)$, $-Z(CON(R^9)_2)$, $-Z(CO_2R^9)$, $-Z(N(R^9)_2)$, $-Z(NR^9CON(R^9)_2)$, $-Z(NR^9(CO)R^9)$, $-Z(NR^9CO_2R^9)$, $-Z(COR^9)$, $-Z(S(O)_pR^9)$ or $-Z(Q)$, wherein each R^9 is independently a hydrogen or (C_1-C_8)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with one or more radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_8)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, R^2 and R^3 is 0-3.

44. The compound of claim 43 wherein A is O, S, S(O), S(O)2, N-H, N-R^4 or CR^4R^7; W is -CN or -C(O)L; wherein L is a halo or C1-C2 alkoxy radical;

R^2 is a hydrogen, halo, $-OH$, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)$alkoxy), $-Z$(aryloxy), $-Z$(aryl), $-Z$(heteroaryl), $-Z((C_3-C_{10})$cycloalkyl), $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$ radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_3-C_8)alkyl, $-((C_1-C_8)alkyl)OH$, $(C_1-C_8)alkoxy-(C_1-C_8)alkyl-$, $-((C_1-C_8)alkyl)N(R^5)_2$, $-((C_1-C_8)alkyl)S(O)_p((C_1-C_8)alkyl)$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$, $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(COR^5)$, $-((C_1-C_8)alkyl)(CO_2R^5)$, $-((C_1-C_8)alkyl)(COR^5)$, $-D'(S(O)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl), $-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^5SO_2R^5)$, $-D'(CON(R^5)_2)$, $-D'(NR^5CON(R^5)_2)$, $-D'(NR^5(CO)R^5)$, $-D'(NR^5CO_2R^5)$, -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), $-D((C_3-C_{10})cycloalkyl)$, $-D(NR^5SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$, $-D(NR^5CON(R^5)_2)$, $-D(NR^5(CO)R^5)$, $-D(NR^5CO_2R^5)$ or $-(NR^5)_k$-D-Q radical;

R^4 is a (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, $-Z((C_1-C_8)alkoxy)$, -Z(aryloxy), -Z(aryl), -Z(heteroaryl), $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or -Z(Q) radical;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH,

halo, $-CF_3$, $-OCF_3$, (C_1-C_8)alkoxy, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, or (C_1-C_8)alkyl radical;

each R^5 and R^7 are each independently a hydrogen, -OH, (C_1-C_8)alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, (C_1-C_8)alkyl or (C_3-C_{10})cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 6;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of R^2, R^3, R^4, R^5 and R^7 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-Z(COOH)$, $-Z(OH)$, $-Z(NO_2)$, $-Z(SH)$, $-(C_1-C_8)$alkyl, $-(C_1-C_8)$acyloxy, $-(C_3-C_{10})$cycloalkyl, $-S-((C_1-C_8)alkyl)_k$-aryl, $-((C_1-C_8)alkyl)_k-SO_2NH$-aryl, $-S-(C_1-C_8)$alkyl, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^9SO_2R^9)$, $-Z(CON(R^9)_2)$, $-Z(CO_2R^9)$, $-Z(N(R^9)_2)$, $-Z(NR^9CON(R^9)_2)$, $-Z(NR^9(CO)R^9)$, $-Z(NR^9CO_2R^9)$, $-Z(COR^9)$, $-Z(S(0)_pR^9)$ or $-Z(Q)$, wherein each R^9 is independently a hydrogen or (C_1-C_8)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with 1-3 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_8)alkyl.

45. The compound of claim 44 wherein A is O, S, N-H or N-R^4; W is -CN or -C(O)L; wherein L is a halo or C1-C2 alkoxy radical;

R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, -Z((C_1-C_8)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C_3-C_{10})cycloalkyl), -Z($NR^{10}SO_2R^5$), -Z($CON(R^5)_2$), -Z($N(R^5)_2$), -Z($NR^{10}CON(R^5)_2$), -Z($NR^{10}(CO)R^5$), -Z($NR^{10}CO_2R^5$), -Z($S(O)_pR^5$) or -Z(Q) radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a (C_3-C_{10})cycloalkyl, (C_3-C_8)alkyl, -((C_1-C_8)alkyl)OH, (C_1-C_8)alkoxy-(C_1-C_8)alkyl-, -((C_1-C_8)alkyl)$N(R^5)_2$, -((C_1-C_8)alkyl)$S(O)_p$((C_1-C_8)alkyl), $-(CH_2)$((C_3-C_{10})cycloalkyl)$_k(CH_2)_m$OH, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_m$OH, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$_k(CH_2)$OH, $-(CH_2)$((C_3-C_{10})cycloalkyl)$_k(CH_2)_m(C_1-C_8)$alkoxy, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_m(C_1-C_8)$alkoxy, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$_k(CH_2)(C_1-C_8)$alkoxy, $-(CH_2)$((C_3-C_{10})cycloalkyl)$_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_mN(R^5)_2$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$_k(CH_2)N(R^5)_2$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_mS(O)_pR^5$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_m(CO_2R^5)$, $-(CH_2)_m$((C_3-C_{10})cycloalkyl)$(CH_2)_m(COR^5)$, -((C_1-C_8)alkyl)(CO_2R^5), -((C_1-C_8)alkyl)(COR^5), -D'($S(O)_qR^5$), -D'(aryloxy), -D'(aryl), -D'(heteroaryl), -D'((C_3-C_{10})cycloalkyl), -D'($NR^{10}SO_2R^5$), -D'($CON(R^5)_2$), -D'($NR^{10}CON(R^5)_2$), -D'($NR^{10}(CO)R^5$), -D'($NR^{10}CO_2R^5$), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), -D((C_3-C_{10})cycloalkyl), -D($NR^{10}SO_2R^5$), -D($CON(R^5)_2$), -D($S(O)_qR^5$), -D($NR^{10}CON(R^5)_2$), -D($NR^{10}(CO)R^5$), -D($NR^{10}CO_2R^5$) or $-(NR^{10})_k$-D-Q radical, provided R^3 is not $-SO_2NH_2$;

R^4 is a (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, $-N(R^5)_2$ or -Z(Q) radical;

wherein each R^{10} is independently a hydrogen or (C_1-C_4)alkyl radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or (C_1-C_4)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4)alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, (C_1-C_4)alkyl or (C_3-C_6)cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 4;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of R^2, R^3, R^4 and R^5 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$acyloxy, $-(C_3-C_6)$cycloalkyl, $-S-((C_1-C_4)alkyl)_k$-aryl, $-((C_1-C_4)alkyl)_k-SO_2NH$-aryl, aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$, $-S(0)_2(C_1-C_4)$alkyl or Q, wherein each R^9 is independently

a hydrogen or (C_1-C_4)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally substituted with 1-2 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or (C_1-C_4)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, R^2 and R^3 is 0-2.

46. The compound of claim 45 wherein A is O, S, N-H or N-R^4; W is -CN or -C(O)L; wherein L is a halo or C1-C2 alkoxy radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(C_1-C_4)alkoxy)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(CON(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(N(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(S(O)_pR^5)$ or $-(NR^{10})_k((C_1-C_2)alkyl)_k$-Q radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)alkyl)OH$, $(C_1-C_4)alkoxy-(C_1-C_4)alkyl-$, $-((C_1-C_4)alkyl)N(R^5)_2$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)OH$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$, $-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl),

-D'((C$_3$-C$_{10}$)cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), -D(NR^{10}SO$_2$R^5), -D(CON(R^5)$_2$), -D(S(O)$_q$R^5), -D(NR^{10}CON(R^5)$_2$), -D(NR^{10}(CO)R^5), -D(NR^{10}CO$_2$R^5) or -(NR^{10})$_k$-D-Q radical, provided R^3 is not -SO$_2$NH$_2$;

R^4 is a (C$_1$-C$_4$)alkyl radical;

wherein each R^{10} is independently a hydrogen or (C$_1$-C$_4$)alkyl radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, -CF$_3$, -OCF$_3$, (C$_1$-C$_4$)alkoxy, -NH$_2$, -NH((C$_1$-C$_4$)alkyl), -N((C$_1$-C$_4$)alkyl)$_2$, or (C$_1$-C$_4$)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C$_1$-C$_4$)alkoxy, -NH$_2$, -NH((C$_1$-C$_4$)alkyl), -N((C$_1$-C$_4$)alkyl)$_2$ or (C$_1$-C$_4$)alkyl radical;

D is -(CH$_2$)$_m$((C$_3$-C$_6$)cycloalkyl)$_k$(CH$_2$)$_m$- and D' is -((C$_1$-C$_4$)alkyl)$_k$-;

Z is (NR^{10})$_k$D or (NR^{10})$_k$D';

each k is independently 0 or 1;
each m is independently an integer between 0 and 3;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of R^2 and R^3 is optionally substituted with 1-2 radicals of halo, -CF$_3$, -OCF$_3$, -OR^9, -SR^9, -NO$_2$, (C$_1$-C$_4$)alkyl, (C$_1$-C$_4$)acyloxy, -NR^{9}SO$_2$R^9, -CON(R^9)$_2$, -CO$_2$R^9, -N(R^9)$_2$, -NR^{9}CON(R^9)$_2$, -NR^9(CO)R^9, -NR^{9}CO$_2$R^9, -COR^9 or

$-S(O)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_4)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, R^2 and R^3 is 0-1.

47. The compound of claim 46 wherein wherein A is O, S or N-H; W is -CN or -C(O)L; wherein L is a halo or C1-C2 alkoxy radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2)alkyl or (C_1-C_2)alkoxy radical;

R^3 is a (C_3-C_6)cycloalkyl, (C_3-C_6)alkyl, $-((C_1-C_4)\text{alkyl})OH$, $(C_1-C_4)\text{alkoxy-}(C_1-C_4)\text{alkyl-}$, $-((C_1-C_4)\text{alkyl})N(R^5)_2$, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mOH$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)OH$, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_m(C_1-C_2)$alkoxy, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(C_1-C_2)$alkoxy, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)(C_1-C_2)$alkoxy, $-(CH_2)((C_5-C_6)\text{cycloalkyl})_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})_k(CH_2)N(R^5)_2$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_5-C_6)\text{cycloalkyl})(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$, -D'(aryloxy), -D'(aryl), -D'(heteroaryl), $-D'((C_3-C_6)\text{cycloalkyl})$, -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k$-D-Q radical, provided R^3 is not $-SO_2NH_2$;

wherein each R^{10} is independently a hydrogen or (C_1-C_2)alkyl radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$, or (C_1-C_2)alkyl radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_2)alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or (C_1-C_2)alkyl radical;

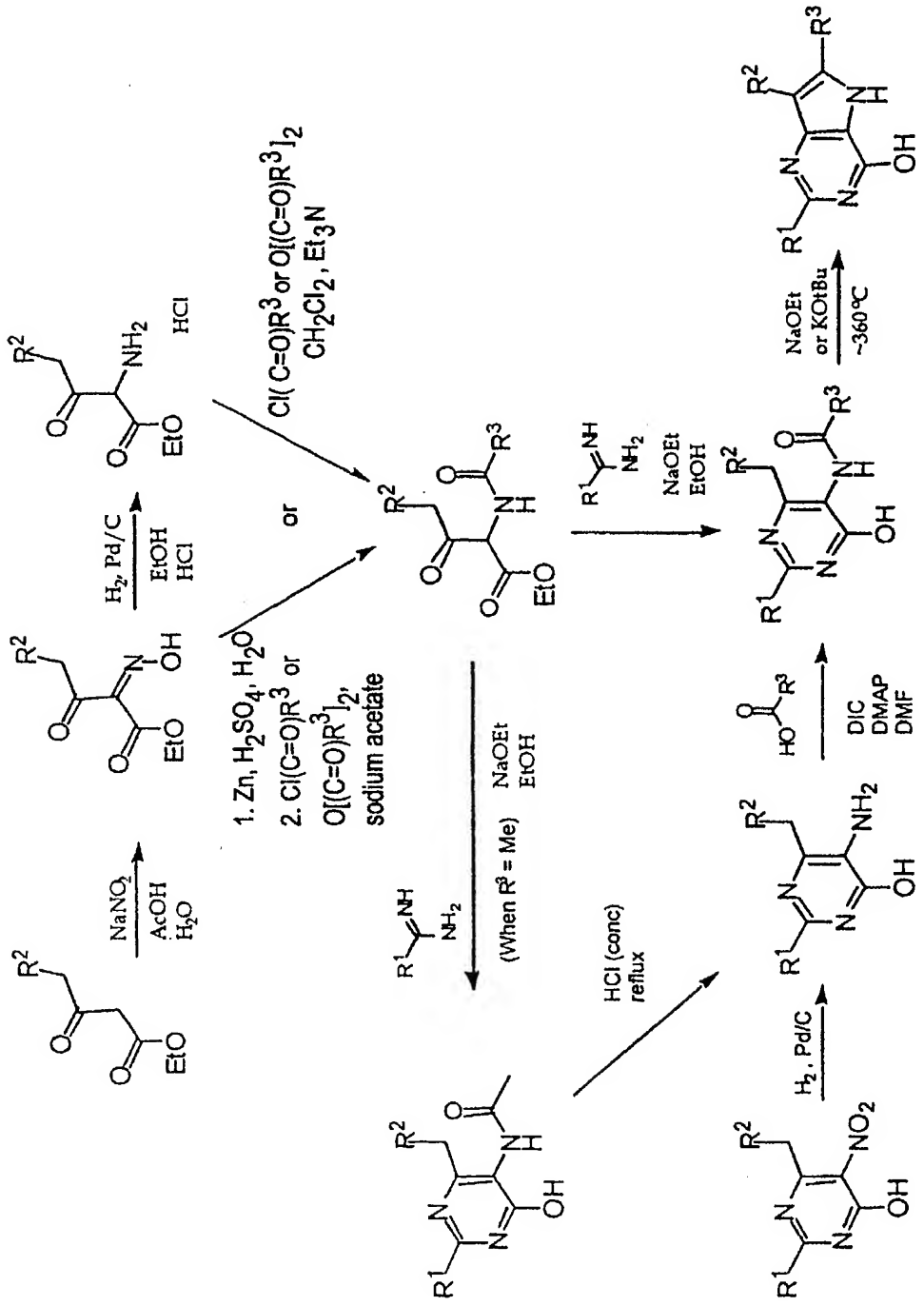
D is $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
each m is independently an integer between 0 and 2;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, (C_1-C_4)alkyl, (C_1-C_4)acyloxy, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(0)_2(C_1-C_4)$alkyl, wherein each R^9 is independently a hydrogen or (C_1-C_2)alkyl radical.

Fig. 1A


NaNO2
AcOH
H2O
H2, Pd/C
EtOH
HCl
HCl
1. Zn, H2SO4, H2O
2. Cl(C=O)R3 or O[(C=O)R3]2,
sodium acetate
or
Cl(C=O)R3 or O[(C=O)R3]2
CH2Cl2, Et3N
(When R3 = Me)
NaOEt
EtOH
HCl (conc)
reflux
NaOEt
EtOH
H2, Pd/C
DIC
DMAP
DMF
NaOEt
or KOtBu
~360°C

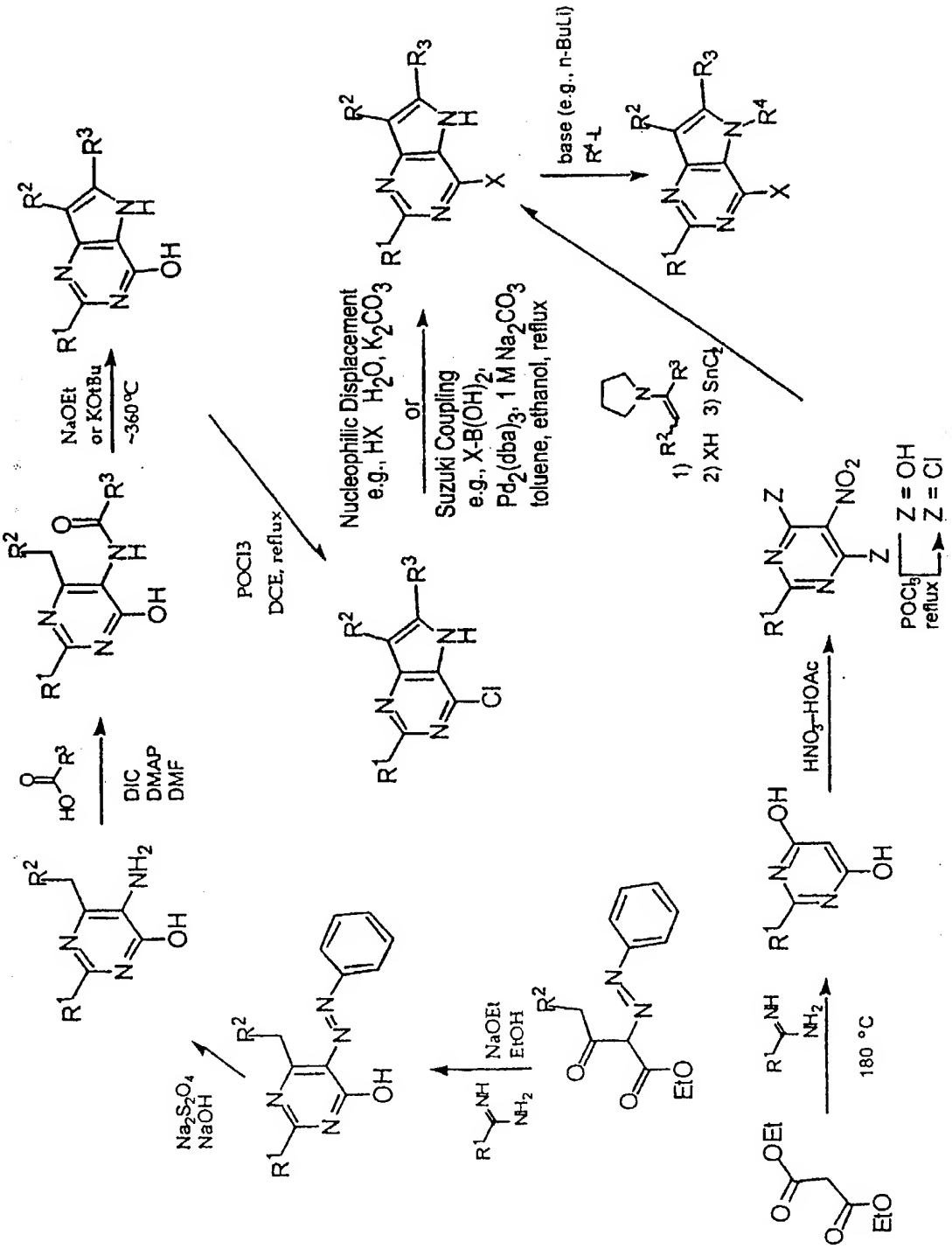

NaOEt or KOtBu ~360°C
DIC DMAP DMF
POCl3 DCE, reflux
Nucleophilic Displacement e.g., HX H2O, K2CO3
or
Suzuki Coupling e.g., X-B(OH)2, Pd2(dba)3, 1 M Na2CO3 toluene, ethanol, reflux
base (e.g., n-BuLi) R4-L
1) 2) XH 3) SnCl2
POCl3 reflux
Z = OH Z = Cl
HNO3–HOAc
180 °C
NaOEt EtOH
Na2S2O4 NaOH

Fig. 1B

Fig. 2

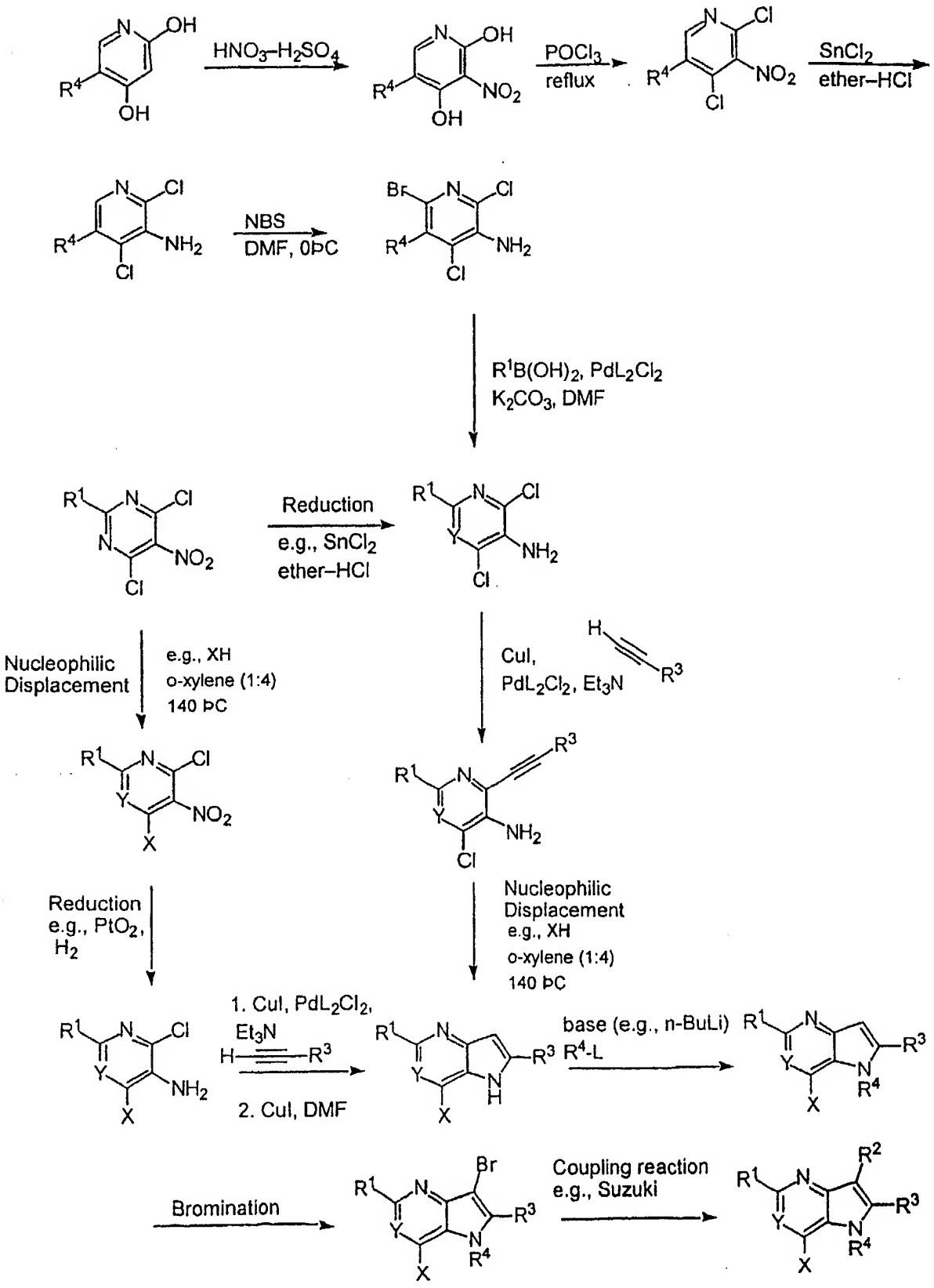

HNO3–H2SO4
POCl3
reflux
SnCl2
ether–HCl
NBS
DMF, 0ÞC
R1B(OH)2, PdL2Cl2
K2CO3, DMF
Reduction
e.g., SnCl2
ether–HCl
Nucleophilic
Displacement
e.g., XH
o-xylene (1:4)
140 ÞC
CuI,
PdL2Cl2, Et3N
Reduction
e.g., PtO2,
H2
Nucleophilic
Displacement
e.g., XH
o-xylene (1:4)
140 ÞC
1. CuI, PdL2Cl2,
Et3N
2. CuI, DMF
base (e.g., n-BuLi)
R4-L
Bromination
Coupling reaction
e.g., Suzuki

Fig. 3

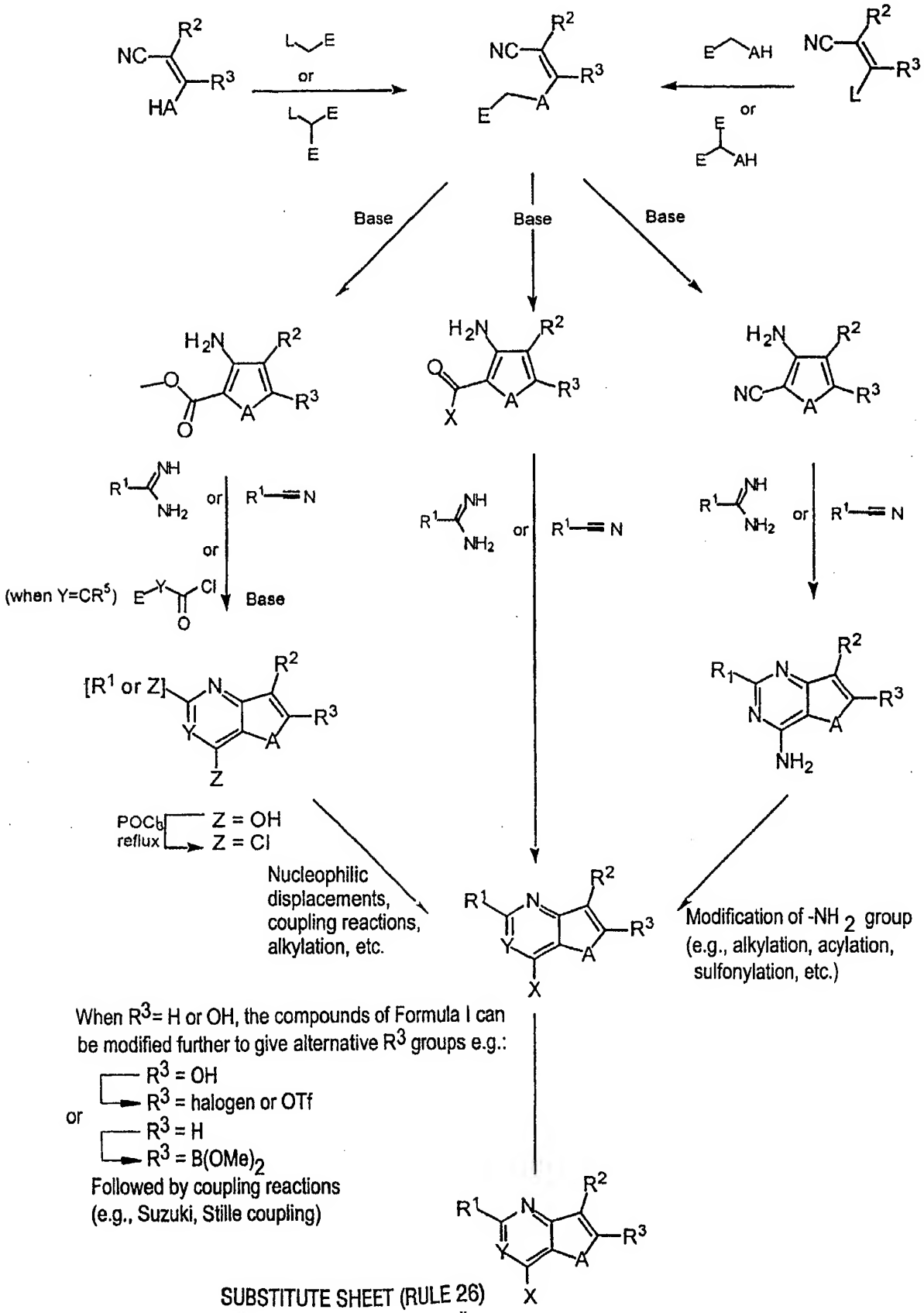
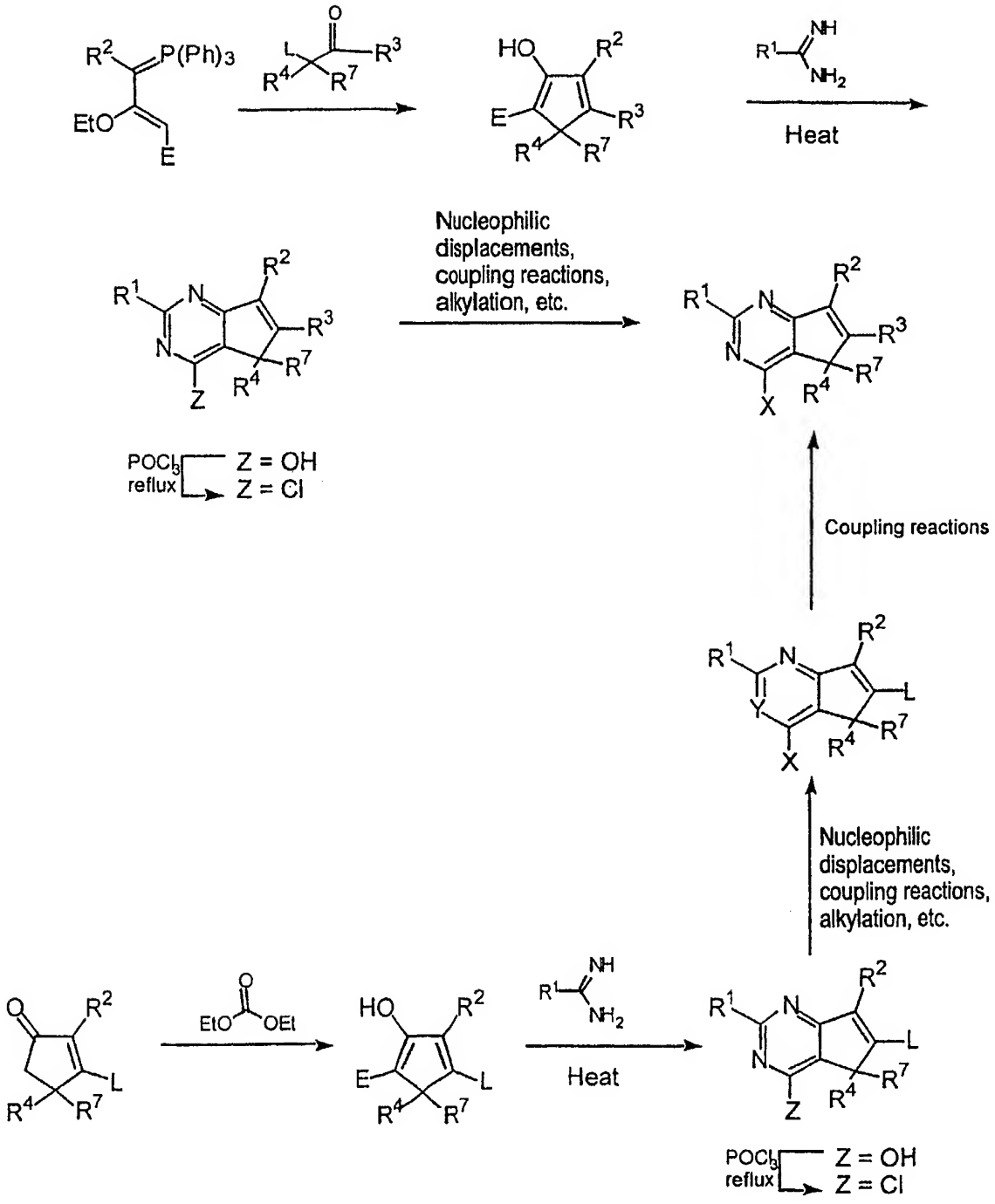

or
or
or
Base
Base
Base
or
or
or
(when Y=CR5)
Base
[R1 or Z]
POCl3 reflux
Z = OH
Z = Cl
Nucleophilic displacements, coupling reactions, alkylation, etc.
Modification of -NH2 group (e.g., alkylation, acylation, sulfonylation, etc.)
When R3= H or OH, the compounds of Formula I can be modified further to give alternative R3 groups e.g.:
R3 = OH
R3 = halogen or OTf
or
R3 = H
R3 = B(OMe)2
Followed by coupling reactions (e.g., Suzuki, Stille coupling)

Fig. 4


Heat
Nucleophilic displacements, coupling reactions, alkylation, etc.
POCl3 reflux
Z = OH
Z = Cl
Coupling reactions
Nucleophilic displacements, coupling reactions, alkylation, etc.
EtO
OEt
Heat
POCl3 reflux
Z = OH
Z = Cl

INTERNATIONAL SEARCH REPORT

Inter ...nal Application No
PCT/US 99/02500

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/44 A61K31/505 A61K31/52 C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 29110 A (JANSSEN PHARMACEUTICA N. V.) 14 August 1997 cited in the application see the whole document ---	1,19,43
Y	WO 97 25041 A (ELI LILLY AND COMPANY) 17 July 1997 see the whole document ---	1,19,43
Y	WO 96 40142 A (PFIZER INC.) 19 December 1996 see page 2, line 30 - page 5, line 30 ---	1,19
Y	WO 96 35689 A (NEUROGEN CORPORATION) 14 November 1996 cited in the application see page 2 - page 3 --- -/--	1,19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 1999	15/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kyriakakou, G

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/US 99/02500

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 778 277 A (PFIZER INC.) 11 June 1997 see the whole document	1,19,43
Y	EP 0 729 758 A (PFIZER INC.) 4 September 1996 see the whole document	1,19
Y	EP 0 682 027 A (CIBA-GEIGY AG) 15 November 1995 see the whole document	1,19,43
P,A	WO 98 07726 A (NOVARTIS AG) 26 February 1998 cited in the application see the whole document	1,19
P,A	WO 98 08847 A (PFIZER INC.) 5 March 1998 cited in the application see the whole document	1,19,43
P,A	WO 98 06703 A (WARNER-LAMBERT COMPANY) 19 February 1998 cited in the application see the whole document	1,19

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ɔnal Application No
PCT/US 99/02500

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9729110 A	14-08-1997	AU 1720997 A	28-08-1997
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INTERNATIONAL SEARCH REPORT

In ..national application No.
PCT/US 99/ 02500

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 27-42
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 27-42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 99/02500

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		NO 990927 A	26-02-1999
WO 9806703 A	19-02-1998	AU 4054197 A	06-03-1998